1
The Immune System

1.1
Introduction

All living things – animals, plants and even bacteria – can act as hosts for infectious organisms and thus have evolved mechanisms to defend themselves against infection. Infection can be by other living things, non-living things (viruses) and possibly even molecules (prions). Since it is so crucial to our own survival, much of our understanding of immunity has come from studies in humans – particularly in relation to the causes and prevention of disease – but deep insights have also come from experimental studies in animals such as mice. For these reasons, in this book we concentrate on the immune systems of humans and mice. These, along with other more recently evolved organisms (e.g. birds and amphibians), have the most complex and sophisticated immune systems, but the origins of these can in many instances be traced back to the most distant and ancient species in evolutionary history.

In this chapter we provide an overview of immunology in which we introduce the key players in immunity, largely focussing on the immune systems of humans and mice. We start by briefly considering how infection can be sensed by the host organism and how it is possible for a host to recognize many very different infectious agents (Section 1.2). We then introduce the tissues and specialized organs where immune responses occur (Section 1.3). To eliminate different infections effectively, immune responses need to be tailored to particular types of infection. This requires a variety of cells and molecules that can interact coherently to generate the mechanisms that are needed to eliminate each type of infection. As these mechanisms help to bring about or "effect" the elimination of infectious agents they are termed effector mechanisms.

Defence against infection is divided into two main forms termed innate immunity and adaptive immunity. Innate defence mechanisms are present in different forms in all multi-cellular organisms, including plants. Adaptive defence mechanisms have evolved more recently in vertebrates. In vertebrates, the interaction of innate and adaptive immune mechanisms is essential for the generation of effective immunity to infection.

To introduce the mechanisms of immunity we start by describing the different types of immune cells and their function in innate and adaptive immunity to infection (Section 1.4). We then introduce the major classes of molecule involved in functions such as the detection of infection, the recruitment of cells to infected sites, communication between cells and tissues, signalling within cells, and, usually, elimination of the infectious agent (Section 1.5).

The immune system that humans have evolved is, however, not perfect and we discuss some of these imperfections at the end of this chapter (Section 1.6). The immune system is a very effective killing machine, and if it goes wrong it can cause severe disease and even death of its host. To cover these latter areas we first consider how the immune system is able to discriminate between what needs to be eliminated and what does not – particularly in the case of adaptive immunity, which has evolved to recognize molecular structures largely at random. We then introduce the different ways in which the immune system can cause damage if it becomes directed not to infectious agents, but to otherwise harmless targets, including many inert substances around us and within the tissues of the host itself. We discuss the problems of transplants (some of which can even attack their hosts) and why the immune system fails to reject malignant tumours (cancer). Finally, we turn from problems to solutions and introduce two areas in which either the intact immune system and components of immunity can be harnessed for our own benefit and from which tools can be derived to treat disease.

By the end of this chapter you should have insight into of the basic properties and functions of the immune system, and will understand the principles of its roles in defence against infectious disease. You will start to have an appreciation of why it is pivotal to life, disease and death, and how it is important not only in prevention of disease but in its causation. This chapter will lead you on to the following chapters where different areas of immunity are discussed in greater depth.

1.2
Host Defence Against Infection

We need immune responses to defend ourselves against infection. Many different kinds of organism have the potential to infect us and, if they do so, can cause us harm in many

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different ways. To deal with all these potential threats we, as hosts for infectious agents, need a variety of different kinds of host defence mechanisms. Indeed this applies for any living organism.

1.2.1 Infectious Agents

To understand how the immune system works in infection we need to know who the aggressors are. Potentially infectious agents include the following:

- Viruses, which are non-living entities. Common examples are influenza virus, human immunodeficiency virus (HIV) and herpes simplex virus (HSV, which can cause cold sores or genital ulcers).
- Bacteria, are single-celled prokaryotic organisms. Examples include *Staphylococcus* and *Streptococcus* that cause acute infections such as abscesses and sore throats, and *Mycobacteria* that cause chronic infections such as tuberculosis and leprosy.
- Fungi, which are unicellular, such as Candida that causes thrush, or multicellular.
- Parasites, which are eukaryotic organisms. Some are single-celled protozoa that cause diseases such as malaria, others are large, multicellular organisms (metazoa) such as tapeworms.

In this book, for convenience, we will sometimes refer to smaller infectious agents, including viruses, as microbes because they are microscopic in size. However, many parasites, the metazoa, are often far from microscopic in size.

1.2.2 Host Defence

All organisms possess mechanisms to defend themselves against infection, and immunity is a specialized form of host defence. In mammals, defence mechanisms can be passive or active. Passive defence comes in the form of natural barriers that hinder infection. Examples are skin, which prevents access of microbes to the underlying tissue, and gastric acid in the stomach which, not surprisingly, can kill many microbes that might be ingested with food. Their existence is quite independent of the presence of infection. Active defence is brought about by immune responses that involve a diversity of different effector mechanisms that are induced by the presence of infection and which may eliminate the microbe. Thus, all forms of active immunity depend on specific recognition of molecules present in the infecting agent. This is turn leads to a response, involving the interaction of cells and molecules to produce different effector mechanisms that can often eliminate the infection.

Immunity is itself divided into two different forms – innate and adaptive. Innate responses occur rapidly and can generate effector mechanisms that are effective within minutes or hours of infection. In contrast, adaptive immunity takes much longer to become effective, usually over a few days. In immunity to most forms of infection, however, both innate and adaptive immunity are essential. A major advantage of adaptive immune responses, not seen with innate immunity, is that they generate memory – a second infection with the same microbe elicits a stronger, faster and usually more effective response. See Figure 1.1.

1.2.3 Immune Recognition

Different types of cells and molecules are involved in the initiation of innate and adaptive immune responses although, as mentioned above, their interaction is essential in defence against most infectious agents. So what do the innate and adaptive arms of immunity do in general terms? Broadly speaking we can view some components of the innate immune system as being involved in the detection of

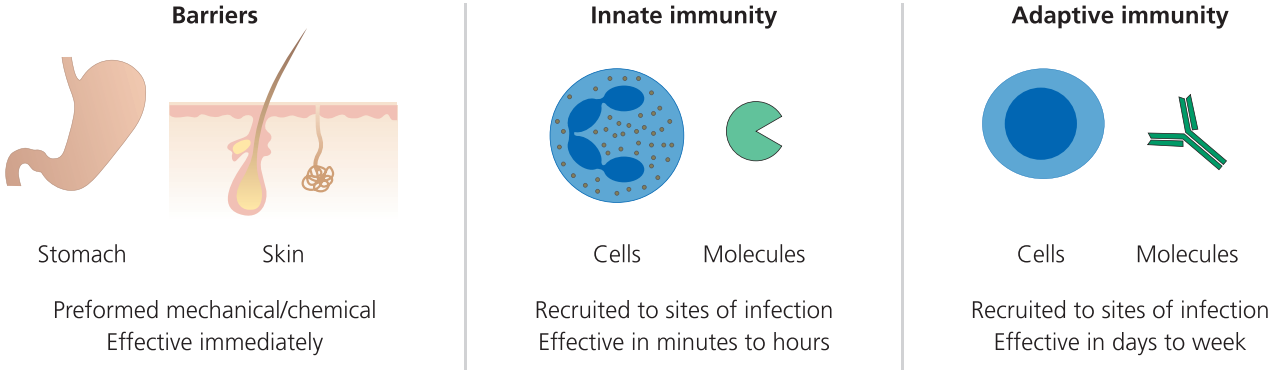

Fig. 1.1 Mechanisms of defence against infection. Natural barriers. These stop infectious agents entering the host or provide a hostile environment. Physical barriers to infection include the epithelia of the skin, lung and airways, and the gastro-intestinal and urogenital tracts. Cells in these barriers may also secrete agents that kill infectious agents. **Innate immunity**. This is the first form of immunity induced by infectious agents. Cells and molecules such as phagocytes and complement can make rapid responses that may eradicate the infection. **Adaptive immunity**. Later adaptive responses may be generated if the infectious agent is not killed by innate immunity. Cells and molecules such as lymphocytes and antibodies take longer to become effective, but adaptive immunity can also lead to a state of long-lasting resistance to re-infection termed **immunological memory** (not shown).

"harmful" things that represent "danger" to the organism, such as general classes of microbes that may have infected the host. Other components then endeavour to eliminate the microbe. In contrast, the adaptive immune system can discriminate very precisely between individual microbes, even of the same type, but can generally only make a response if it has been informed by the innate system that what is being recognized is "dangerous". If so, adaptive responses may then help to eliminate the microbe, if it has not already been eradicated during the earlier innate response. Recognition of infectious agents is essential for any form of immunity and thus for host defence against them. Generally speaking, the types of receptors used for recognition differ in innate and adaptive responses. See Figure 1.2.

1.2.3.1 Recognition in Innate Immunity: Pattern Recognition Receptors

The key components of the innate immune system include cells such as phagocytes and soluble molecules such as complement. These work together to sense the presence of infection. The recognition of potentially dangerous microbes usually leads to the generation of inflammation, familiar to us all. One way of viewing this is that the innate immune systems of multi-cellular organisms can generate "alarm" signals in response to danger, and that some of these signals cause inflammation. Alarm is not a conventionally used term, but is one that we find helpful and therefore will use it from time to time in this book. Inflammation enables effector cells and molecules to be targeted to the site of infection. As noted

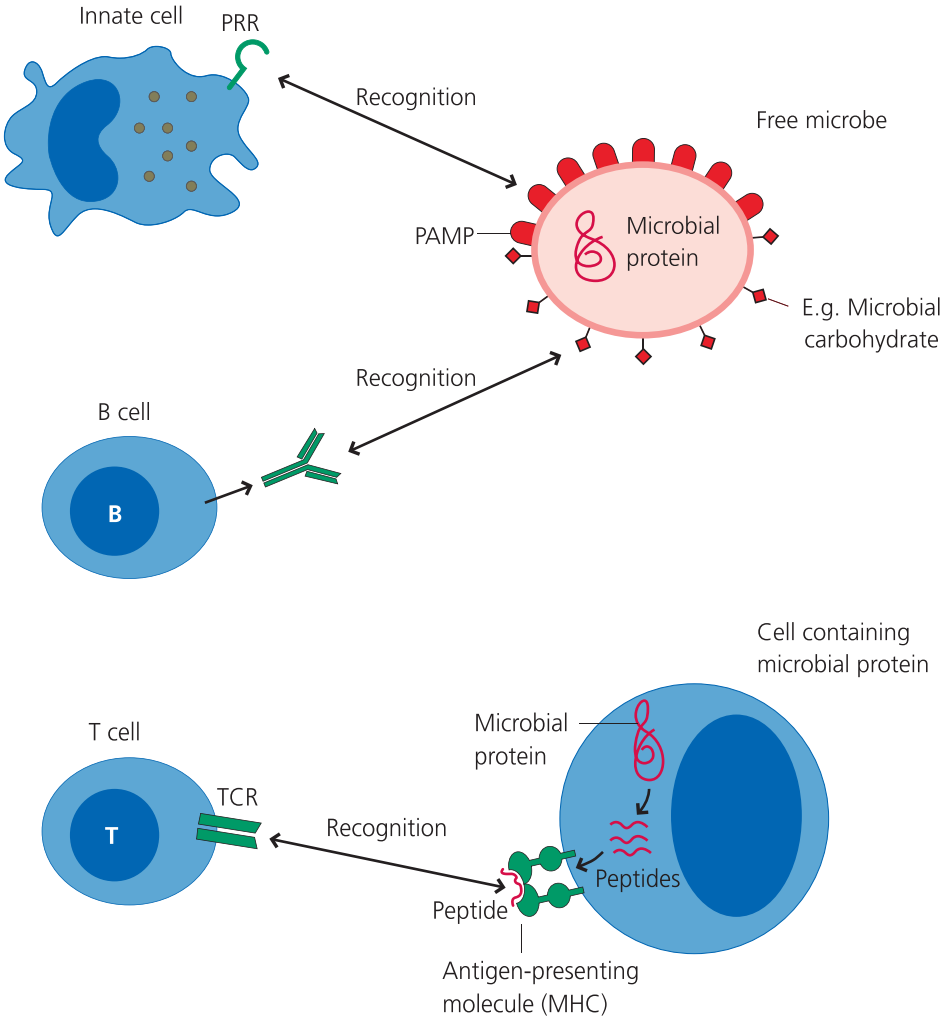

Fig. 1.2 Immune recognition. Innate immunity. PRRs directly or indirectly recognize conserved features of infectious agents called PAMPs. PRRs are widely expressed throughout the innate immune system. **Adaptive immunity.** The two main types of lymphocytes, B cells and T cells, have highly discriminatory receptors for microbial components or antigens, BCRs and TCRs respectively. These recognize antigens in totally different ways. BCRs can be secreted as soluble antibodies and bind to different types of antigen, such as carbohydrates on glycoproteins in their unfolded, native form. In contrast, TCRs generally recognize small peptides, generated by degradation of microbial proteins, in association with specialized presenting molecules (MHC molecules) on the surface of other cells (i.e. as peptide–MHC complexes).

above, other signals generated during innate responses can also determine whether, and in what way, the lymphocytes of adaptive immunity will respond.

The recognition of infectious agents in innate immunity is mediated by germline-encoded receptors called pattern recognition receptors (PRRs). These receptors generally recognize conserved features of infectious agents that are often shared by different classes of microbes, these microbial features are called pathogen-associated molecular patterns (PAMPs). PAMPs directly or indirectly stimulate innate immune responses by acting as agonists for PRRs. An agonist is anything that stimulates a response through a receptor, as opposed to an antagonist that inhibits it. PAMPs may bind directly the PRRs, therefore acting directly as ligands for these receptors, but some PAMPs can trigger responses by binding to a different molecule that then associates with a PRR, so it is useful to use the general term agonist. This also allows us to discriminate clearly between components of microbes that trigger innate responses, and molecular structures which are recognized in adaptive immunity that are termed antigens (below).

The cells responsible for initiating activation of the innate immune system are widely distributed in tissues and organs, and they possess many copies of different types of PRR that trigger rapid responses. This allows very rapid activation and deployment of the effector mechanisms of innate immunity. In many cases the innate system can eliminate the infectious microbe, often without any symptoms occurring (i.e. subclinically), and if there has been damage to the tissues at the site of infection the innate system will initiate repair and healing. Importantly, activation of the innate system is also essential for the triggering of adaptive immune responses

1.2.3.2 Recognition in Adaptive Immunity: Antigen Receptors

The key components of the adaptive immune system are the lymphocytes. It is convenient at this stage to divide these into two main groups (other types do exist). One group is the T lymphocytes (T cells) which have evolved to interact with other cells. The other is the B lymphocytes (B cells) which are the precursors of cells that can make soluble antibodies. The recognition of molecules from infectious agents by lymphocytes is mediated by their specialized antigen receptors, which are not present on cells of innate immunity. An antigen can be defined as a molecular structure against which a specific adaptive immune response can be made. In contrast to PRR agonists in innate immunity (above), the antigens which stimulate lymphocyte responses are generally unique to particular infectious agents no matter how closely they are related.

Collectively, lymphocytes express a vast range or repertoire of antigen receptors of different specificities, but each lymphocyte expresses multiple copies of a receptor of only a single given specificity. The term specificity relates to the particular antigen(s) that each lymphocyte is able to recognize. These receptors are generated by rearrangement of germline DNA, a process that is not known to occur for any other type of molecule. Their specificity is generated largely at random and in advance of any infection. Lymphocyte recognition of antigen is thus anticipatory. Lymphocyte antigen receptors are highly discriminatory and distinguish between even very small differences in antigens, such as an amino acid substitution in a peptide or a specific side chain in an organic molecule.

The vast repertoire of T and B cell antigen receptors means that a lymphocyte expressing a particular receptor is exceedingly rare. In addition, lymphocytes are normally small, relatively inactive cells. Thus, adaptive immune responses require the activation and proliferation of specific clones of B cells or T cells in order to reach a critical mass that can deal with the infectious agents and this takes time. Adaptive responses also need to generate the particular effector mechanisms that are most suited to eliminate the infection and this also takes time. Hence, adaptive immune responses are generally slower to be triggered than innate responses. However, following infection, increased numbers of antigen-specific lymphocytes remain in the body and these provide stronger, more rapid responses should re-infection occur.

1.2.3.3 Types of Recognition in Innate and Adaptive Immunity

Earlier, we suggested that some components of innate immunity can be viewed as recognizing danger, and that in general they are able to discriminate between harmful and harmless stimuli. Danger can be represented by the presence of an infectious agent or by signs of cell damage or stress that may or may not be associated with infection. In contrast, the antigen receptors of lymphocytes enable them to discriminate very precisely between what is "self" (any normal component of the host) and "non-self" (such as a component of a microbe), but not between harmless and harmful. Therefore, it is primarily the signals generated by the innate system that inform lymphocytes as to whether the antigens that they are recognizing originate from harmful or harmless agents, and hence determine whether or not these lymphocytes become activated and also precisely how they need to be activated in the context of the specific danger that is posed. If they are instructed that there is no danger (or not instructed that there is danger), then lymphocytes become unresponsive, or "tolerant", to what they are recognizing (Section 1.6.1).

1.2.4 Stages of Immunity

Immune responses to infectious agents involve a sequence of events that usually occur in distinct anatomical compartments. Immunologists divide tissues into lymphoid tissues, on one hand, and non-lymphoid or peripheral tissues, on the other. As we shall see (below), lymphocytes are produced in primary lymphoid tissues, but tend to localize in specialized sites, the secondary lymphoid tissues. In contrast, the cells of innate immunity are distributed throughout all tissues and organs. Once the natural barriers are breached by an infectious agent, innate agonists such as PAMPs, derived from the infecting agent, trigger the activation of innate immunity. Infections most commonly start in peripheral, non-lymphoid

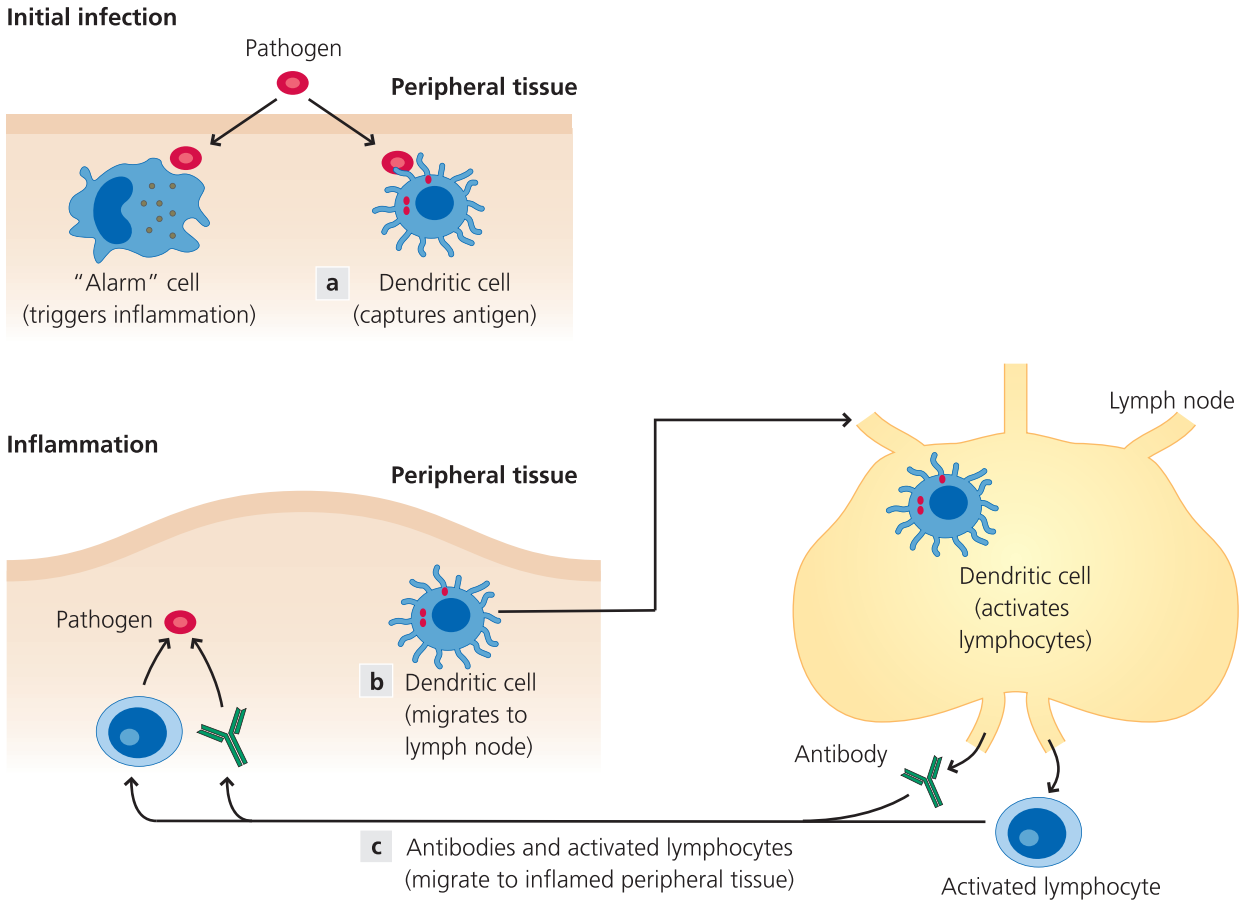

Fig. 1.3 Stages of immunity. Innate and adaptive immunity are closely interlinked. Specialized local ("alarm") cells of innate immunity can sense the presence of infectious agents. Consequent inflammation enables blood-borne innate effector cells and molecules to enter the tissue. (a) Dendritic cells (DC) at the site of infection sense the presence of an infectious agent and capture molecules (antigens) from it. (b) They migrate into secondary lymphoid tissues and activate lymphocytes that are specific for the infectious agent. (c) Some lymphocytes then make **antibodies** that circulate in blood to the site of infection and attack the infectious agent; other lymphocytes enter sites of infection and help or recruit other cells to kill the infectious agent, or directly kill infected cells.

tissues, and it is the resident innate cells such as macrophages and mast cells in these tissues that first recognize innate agonists. The subsequent inflammatory response is then crucial for the rapid recruitment of other innate effector cells and molecules, such as specialized phagocytes and complement, into the site of infection to help eliminate the microbes that are present there.

Adaptive immunity is also initiated by the infection and becomes evident a few days to a week later. For this to happen, antigen needs to be transported to secondary lymphoid tissues (e.g. to lymph nodes or spleen; below) during the innate phase so that it can be recognized by lymphocytes that tend to congregate in these organs. The molecules responsible for antigen recognition are the respective antigen receptors of the two main groups of lymphocytes: T cell receptors (TCRs) and B cell receptors (BCRs, that can later be secreted as antibodies). The activated lymphocytes then either become effector cells themselves (e.g. some T cells develop into cytotoxic cells that can kill virally infected cells, or B cells develop into plasma cells that secrete antibodies) or they can recruit and activate other effector cells at the site of infection, often including cells of innate immunity. Together, these different effector mechanisms, which are recruited into sites of infection because of inflammation, in most cases control and ultimately clear the infection. Finally, as noted above, in most forms of adaptive immunity, memory lymphocytes are generated in lymphoid tissues. Once induced, memory T and B cells localise to non-inflamed peripheral tissues or secondary lymphoid organs and, in the case of re-infection with the same organism, generate rapid, stronger adaptive responses. See Figure 1.3.

1.3 Anatomical Basis of Immunity

Immune responses occur in complex living organisms. Infection has driven the evolution of tissues and organs in which these responses take place. To understand immune responses requires an understanding of the structure of these tissues and organs in relation to their immune functions. For the

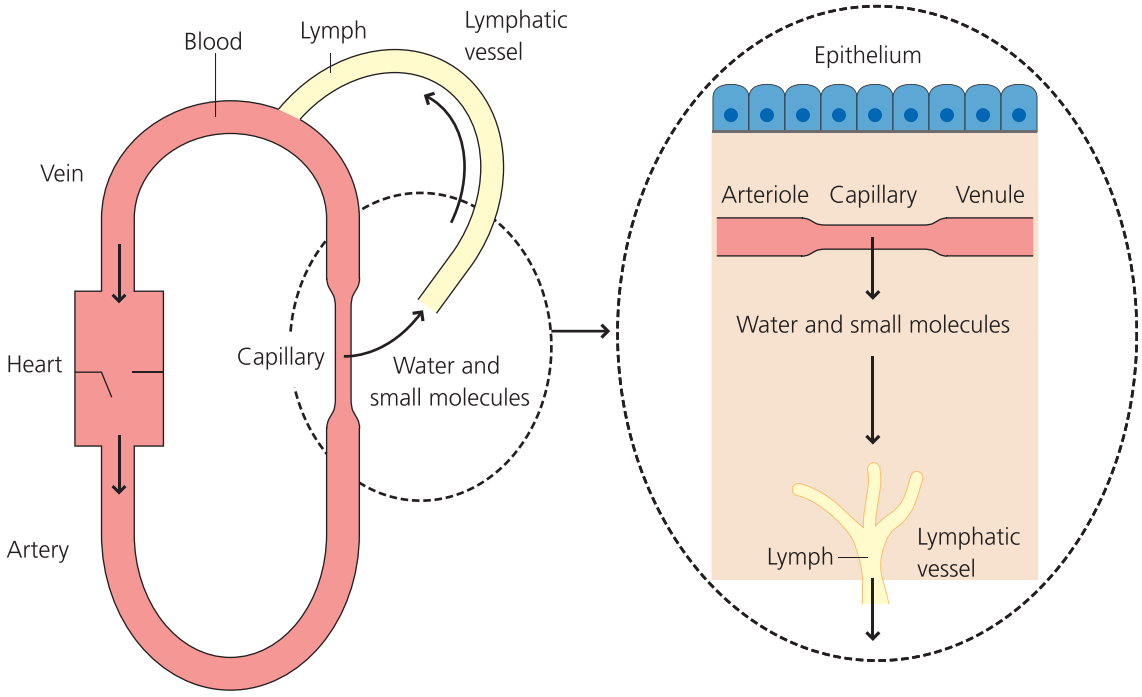

Fig. 1.4 Blood and lymph. Blood transports water, oxygen and small molecules that diffuse into extravascular tissues across endothelial cells of small blood vessels. Blood also carries leukocytes (white blood cells), but these cells, and larger molecules such as antibodies, can only enter tissues in large amounts at inflammatory sites (Figure 1.3). Extravascular fluid collects into lymphatic vessels and ultimately re-enters blood. Lymph also transports cells from sites of infection into lymph nodes, enabling adaptive immunity to be triggered (Figure 1.3).

benefit of readers who have little or no background in anatomy and histology we will first give a very general introduction to this area.

1.3.1 Peripheral Tissues

For immunologists, peripheral tissues refer to most tissues and organs of the body. They exclude primary and secondary lymphoid organs (below). A generalized tissue or organ is covered by an epithelium, a continual layer of cells that is often in contact with the external environment. Examples are the outer layers of the skin, and the lining of the gastro-intestinal, respiratory and urogenital tracts. Underlying the epithelium there is usually a basement membrane and under this lies loose connective tissue containing cells such as macrophages, mast cells and fibroblasts, and structural components such as collagen fibres (e.g. Figure 1.10).

All tissues and organs are vascularized they have a blood supply. It is crucial for water and solutes, such as nutrients and dissolved oxygen, to be able pass through the linings of blood vessels into the surrounding tissues, so that the cells in these extravascular sites can be nurtured and maintained. This extravascular fluid with its solutes then needs to be collected, as lymph, and returned back into the blood. Therefore, all tissues and organs contain vessels of two types: blood vessels and lymphatics (see Figure 1.4).

Blood leaving the heart is brought to tissues by arteries, which subdivide to form arterioles and ultimately capillaries. The latter are the sites where molecules normally diffuse into and from extravascular tissues. Capillaries join to form venules, these are the vessels where cells migrate into tissues under both normal and inflamed conditions. The capillarity then join to form venules that join to form veins, which ultimately return the blood to the heart. Lymphatics originate from blind endings in tissues. They collect molecules as well as motile cells from the extravascular spaces in tissues and transport them to lymph nodes in afferent lymph. Lymph nodes serve as filters and are sites where adaptive immunity can be initiated. Efferent lymph, leaving the lymph nodes, then carries cells and molecules into larger vessels. The main one is the thoracic duct, which then drains back into the blood.

During immune responses the blood acts as a delivery system. Blood vessels and lymphatics are lined by flattened endothelial cells. The blood transports leukocytes, which are the white blood cells as well as erythrocytes, which are the red blood cells (RBCs). If molecules on the plasma membranes of leukocytes recognize complementary molecules on the endothelium, they can adhere to it and may subsequently migrate into the extravascular spaces of the local tissue. As noted above, some small molecules can normally diffuse freely out of the blood in capillaries and venules, but most macromolecules are retained in the blood. Such macromolecules can, however, be delivered selectively to sites of inflammation because gaps open up between venule endothelial cells at these sites (e.g. Figure 1.6).

Some tissues are called “mucosal”. In general, but not always, this is because their epithelia contain goblet cells

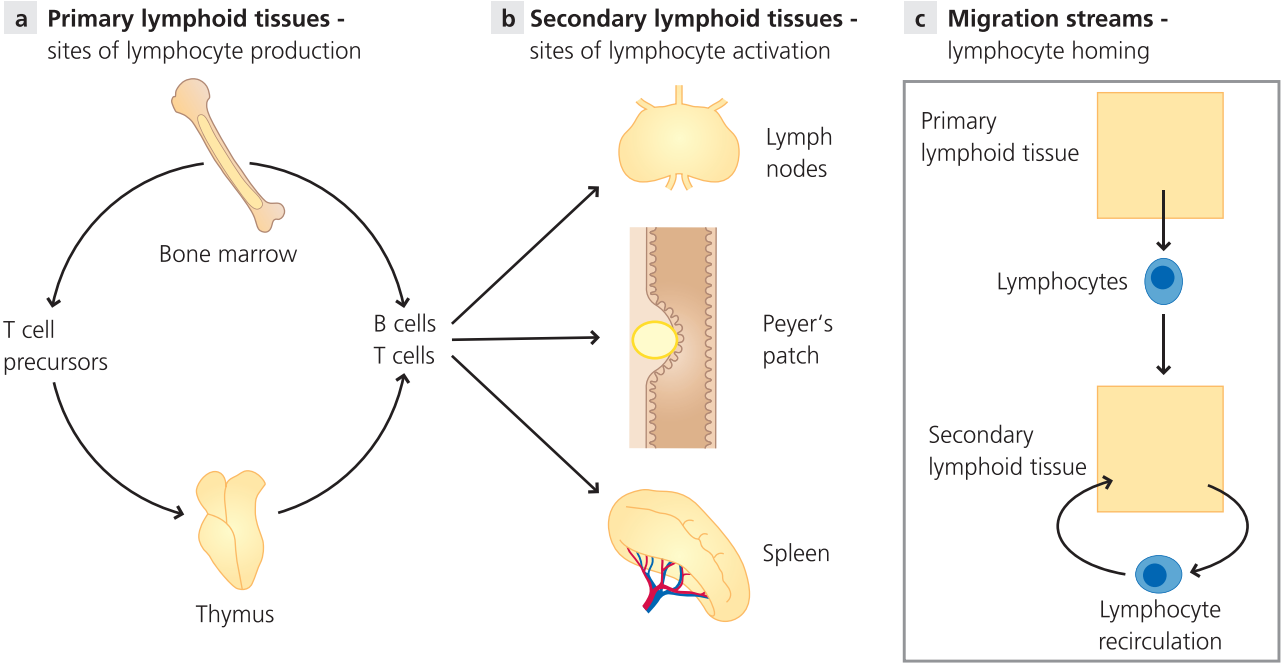

Fig. 1.5 Primary and secondary lymphoid tissues. (a) Primary lymphoid tissues are sites where lymphocytes are produced. In adult humans and mice the main sites are the *bone marrow* and the *thymus*, where B cells and T cells, respectively, undergo most or all of their development. (b) **Secondary lymphoid tissues** or organs are sites where adaptive responses are induced and regulated. The main tissues are lymph nodes, the spleen and specialized MALTs such as the Peyer's patches in the small intestine. All have highly organized areas containing T cells and B cells. Lymphocytes recirculate between blood and lymph and can monitor different anatomical compartments for infection and mount appropriate responses.

which secrete mucus onto the epithelial surface; mucus acts as a lubricant and as a barrier to infection. Mucosal tissues include the gastro-intestinal tract, the respiratory and urogenital tracts, the eye, and the lactating mammary gland. From an immunological point of view mucosal tissues are important because they are associated with immune responses that differ in important respects from those associated with other peripheral tissues.

1.3.2 Lymphoid Tissues

Lymphoid tissues are those whose major functions are associated with adaptive immune responses. Primary lymphoid tissues are sites where lymphocytes are produced. In adult humans they include the bone marrow and a specialized organ called the thymus, which is the organ in which T cells develop. The bone marrow is also the site where other leukocytes are generated, such as monocytes (which can develop into macrophages) and granulocytes (which are themselves of different types). The process of generating blood cells is called haematopoiesis (below), so the bone marrow can also be termed a haematopoietic organ. In contrast, the secondary lymphoid tissues are the sites where adaptive immune responses are initiated and regulated. These tissues include lymph nodes, which are distributed throughout the body, and the spleen. There are also specialized secondary lymphoid tissues associated with mucosaecalled mucosal-associated lymphoid tissues (MALTs), such as Peyer's patches in the small intestine and the tonsils and adenoids in the throat and nose. See Figure 1.5.

1.3.3 Inflammatory Sites

Usually, recognition of infection in a peripheral site by the innate immune system leads to local inflammation. This is clinically evident as reddening, heat, swelling and pain at the site of infection. One of the main functions of inflammation is to ensure that the cells and molecules needed to deal with the infecting agent are delivered to the right place at the right time. These include, for example, specialized phagocytes and complement components and, often later, lymphocytes and antibodies.

If the infectious agent can be eliminated rapidly (within days or a week or so) the response is known as acute inflammation, and repair and healing of the tissue follows. Typical examples known to almost everyone are abscesses (boils) and sore throats. If, however, the infectious agent persists, continuing inflammation, termed chronic inflammation, leads to continuing tissue damage. This is typically seen with infections such as tuberculosis which may persist for months or years (See Figure 1.6).

More distant sites can also be affected by inflammation at sites of infection, these changes are called the systemic effects of inflammation. Thus, the bone marrow can be stimulated to produce more leukocytes, the liver to produce larger amounts of soluble effector molecules that can

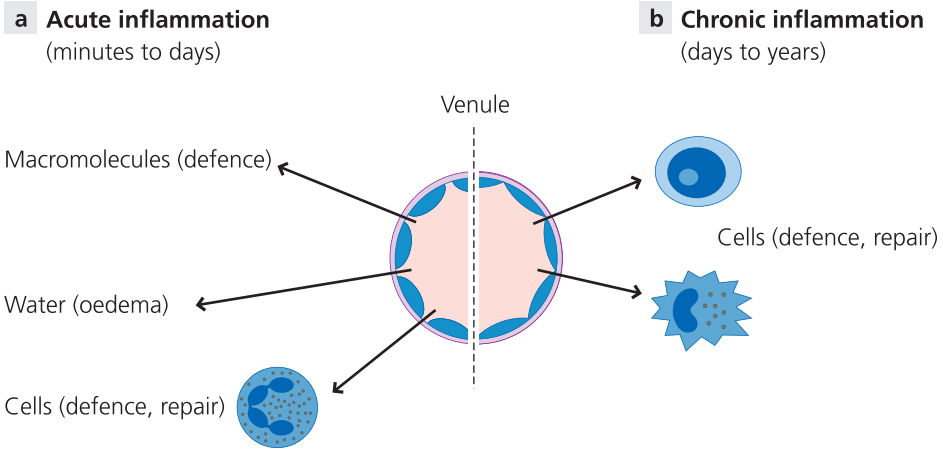

Fig. 1.6 Acute and chronic inflammation. (a) Acute inflammation. Infectious agents such as extracellular bacteria trigger inflammation that starts quickly and lasts a relatively short time. The main features are recruitment of cells and molecules such as neutrophils and complement, and the accumulation of extravascular fluid (oedema). (b) **Chronic inflammation**. Infectious agents that are not quickly eliminated and which trigger adaptive immune responses can lead to chronic inflammation that can last much longer. The main features are recruitment of blood monocytes, which become macrophages, and activated lymphocytes, especially T cells, and sometimes the development of long-lasting granulomas.

contribute to eliminating the infectious agent and the hypothalamus in the brain to induce fever.

1.4 Cellular Basis of Immunity

The primary function of the immune system is to eliminate infectious agents that have breached the natural barriers. This is brought about by the integrated actions of different cells and molecules that, directly or indirectly, lead to recovery from infection. It is the effector cells and molecules that actually bring about the elimination of infectious agents. To simplify understanding; we focus first on the cellular basis of immunity, before turning to molecules involved in immunity in Section 1.5. This is an artificial distinction, since cells and molecules are usually both involved in immune responses, as will be seen in the rest of this book.

1.4.1 Origin of Immune Cells

1.4.1.1 Haematopoiesis

Haematopoiesis is the name given to blood cell development. In the adult mammal this takes place primarily in the bone marrow (also a primary lymphoid tissue), but in the foetus this happens in the liver. The earliest cells in haematopoiesis are the multi-potential stem cells, which can give rise to any and all blood cells. When cells divide each of the progeny cells is usually of the same type. Stem cells are unusual in that the one of the progeny cells is another stem cell, thus maintaining this population, while the other can start to differentiate into a different cell type, ultimately producing all the cells of different lineages.

Initially stem cells divide to form cells that can either give rise to different types of "myeloid" cells or "lymphoid" cells – these are the common myeloid progenitor(CMPs) and common lymphoid progenitors (CLPs). In turn, the former precursors can ultimately produce monocytes and macrophages, different types of granulocytes, and other cells including erythrocytes (RBCs), megakaryocytes (the precursor of blood platelets) and some DCs. In contrast, the latter give rise to the lymphocytes (T cells and B cells) as well as natural killer (NK) cells and other DCs. The development of cells in each pathway is regulated by growth factors that are more or less restricted in their activities. Thus, interleukin (IL)-3 and stem cell factor (SCF) stimulate stem cells which can develop into many different lineages, granulocyte macrophage colony-stimulating factor (GM-CSF) preferentially stimulates development of monocytes, granulocytes and some DCs, and erythropoietin stimulates red cell development. See Figure 1.8.

1.4.1.2 Lymphopoiesis

The term lymphopoiesis refers to the generation of lymphocytes, in contrast to myelopoiesis which refers to generation of myeloid cells (above), and thus can be viewed as a subset of haematopoiesis. In the adult, common lymphoid precursors are present in the bone marrow. B cells start to differentiate in the bone marrow and are released as partially mature (transitional) B cells into the blood. T cell precursors, however, migrate directly to the thymus and T cells complete their development in this organ (a primary lymphoid tissue). It is important to realize that lymphocytes can also undergo further rounds of division and development outside the primary lymphoid organs. This normally happens after they have recognized the antigens for which they are specific, such as molecular components of infectious agents and occurs in organs such as lymph nodes, spleen and Peyer's patches (secondary lymphoid organs). The phenomenon of clonal expansion is an essential feature of adaptive immune responses for it enables clones of specific lymphocytes to

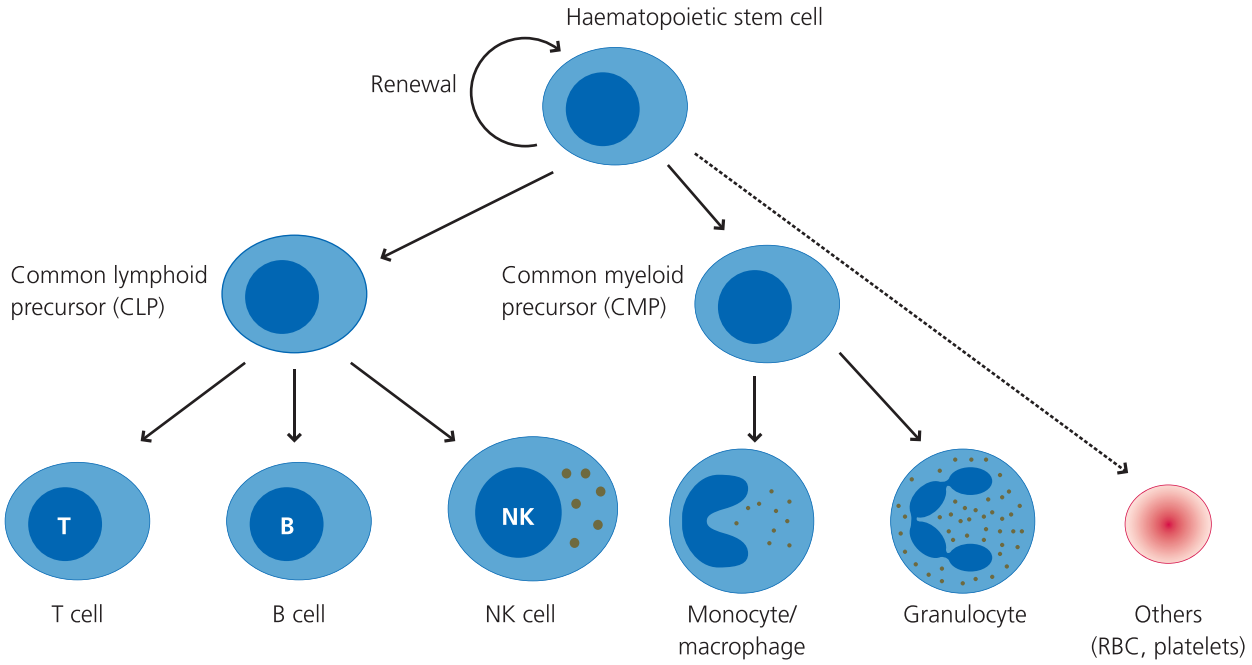

Fig. 1.7 Haematopoiesis. All blood cells are formed from haematopoietic stem cells. On division they form another stem cell (self renewal) and a more committed precursor for a blood cell. In turn, the CLP gives rise to different types of lymphocyte as well as natural killer (NK) cells, while the CMP can generate monocytes and macrophages, granulocytes, and other cell types. The production of different blood cells is regulated by different growth factors and is largely under feedback control.

expand and reach a critical mass that can now help to deal effectively with eliminating the infection.

1.4.1.3 Cell-Mediated Immunity

The principal mechanisms by which cells can help to defend against infection are the following:

i) Killing the microbe directly (e.g. bacteria are often taken up and killed intracellularly by phagocytes).
ii) Killing the cells that harbour microbes (e.g. killing of virally infected cells to prevent the release of new viruses).
iii) Preventing access to, or expelling the microbe from, the body and providing defence against larger parasites such as worms in the gut.

These cellular responses, which contribute to cell-mediated immunity as a whole, need to be tightly regulated and coordinated and, quite often, different cells need to collaborate to help to bring about an overall response that lead to the elimination of an infectious agent. See Figure 1.8.

1.4.1.4 Introduction to Cells of the Immune System

The different cells of the immune system can be classified according to overlapping principles. The most important classification is functional – what do they do? This relates to other aspects – their developmental origins and relationships, and their anatomical distribution in the body. Cells are also classified by their morphology, but this can be misleading – naïve B and T cells look more or less the same under the light microscope – and it is more accurate to combine morphology with other approaches such as identification of the surface molecules that the cells express. Based on the these criteria we will now briefly introduce the major groups of cells involved in immune responses before discussing each in more detail. We will divide the cells into those primarily thought of as belonging to innate immunity and those of adaptive immunity, while emphasizing that in reality there is much overlap between the two groups.

1.4.1.5 Cells of Innate Immunity

Macrophages These are divided into two main types:

- Resident macrophages are present in steady-state tissues (i.e. before infection occurs) and can detect the presence of microbes. In turn they can help to trigger inflammation.
- Recruited (or elicited) macrophages are not tissue-resident cells, but they develop from circulating precursors called monocytes that can be recruited into sites of infection. After development into macrophages they can act as effector cells to help eliminate the infection.

Macrophages are one of the two main types of specialized phagocyte that can engulf and internalize (phagocytose), and subsequently kill microbes such as bacteria.

Mast Cells These cells also reside in steady-state tissues and can detect the presence of microbes. Mast cells contain granules that are discharged when they are stimulated, and the granule contents can contribute to triggering of local inflammation.

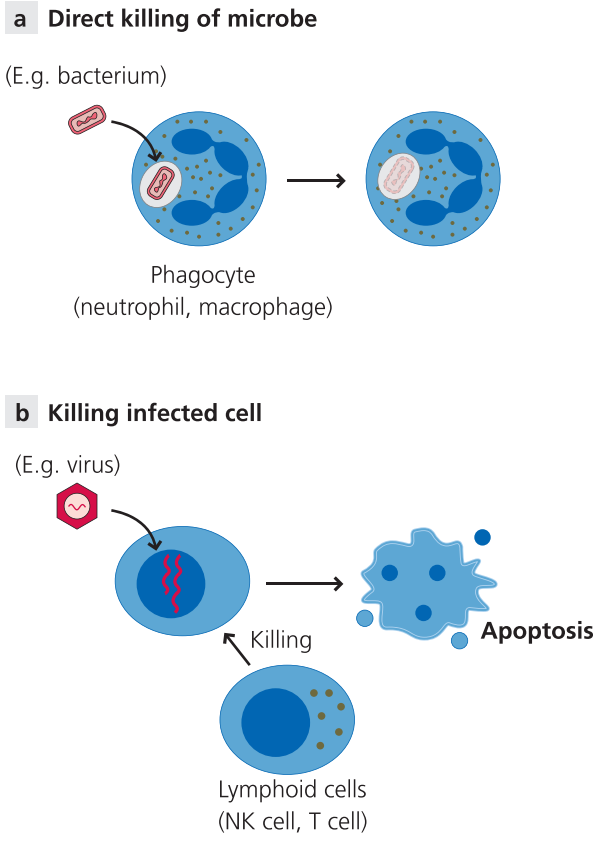

Fig. 1.8 Mechanisms of cell-mediated immunity. There are three main ways in which cells can eliminate infectious agents or protect against infection. (a) **Direct killing**. Specialized phagocytes, mainly macrophages and neutrophils, can internalize microbes such as bacteria and destroy them intracellularly. (b) **Killing of infected cells**. NK cells and cytotoxic T cells can kill infected cells, preventing the replication and release of microbes such as viruses. (c) **Maintaining natural barriers**. Larger parasites, such as intestinal worms, cause damage to the epithelium, risking entry to the body. Cells such as eosinophils can help to repair the damage and, in some cases, may help to expel the organisms or kill it by secreting toxic substances.

Granulocytes These are the major populations of blood leukocytes, the circulating white blood cells. They are called granulocytes because they contain cytoplasmic granules that are visible under the light microscope. They have nuclei that possess two or more lobes, and are thus also called polymorphonuclear leukocytes to distinguish them from monocytes and lymphocytes, the mononuclear leukocytes, which do not have lobulated nuclei. Granulocytes are divided into three groups derived from a common precursor: neutrophils, which are abundant in blood and are a very important type of phagocyte; the rarer eosinophils, and the basophils that are somewhat related to mast cells in function. A crucial feature of granulocytes is that they normally circulate in the blood but can be recruited selectively into inflammatory sites in response to different types of infection. (Note that although mast cells also contain granules, they do *not* circulate in the blood in a mature form and are therefore by definition *not* included in the term granulocyte; they may also originate from a distinct progenitor.)

NK Cells NK cells are developmentally related to lymphocytes, but differ in many aspects from them. NK cells are present in tissues as resident cells and can also be recruited to sites of inflammation. They can kill other cells, such as virally infected cells (i.e. they have cell-killing (cytotoxic) activity) and they also regulate immune responses.

1.4.1.6 Cells of Adaptive Immunity

Lymphocytes These are the primary cells involved in adaptive immune responses. As noted earlier, they have highly discriminatory antigen receptors and are divided into two main groups: B cells and T cells. B cells are the precursors of plasma cells that secrete antibodies. T cells are themselves divided further into two main groups: CD4 T cells that function principally as regulator and coordinator cells in adaptive immune responses, and CD8 T cells that can develop into cytotoxic cells with the capacity to kill cells infected with viruses or other microbes. Cytotoxic T lymphocytes (CTLs) and NK cells, noted above, are the two main types of cytotoxic cells in the immune system.

1.4.1.7 Cells that Directly Link Innate and Adaptive Immune Responses

DCs are another cell type, which actually exist as several subgroups. Most of these are involved in the initiation and regulation of adaptive immune responses. They can be viewed as linking innate and adaptive immunity because they respond quite rapidly to the presence of infection and subsequently change their properties so they can activate lymphocytes, particularly the CD4 T cells.

1.4.2 Phagocytes

All cells in the body are capable of sampling their extracellular milieu in a general process called endocytosis. They may do so

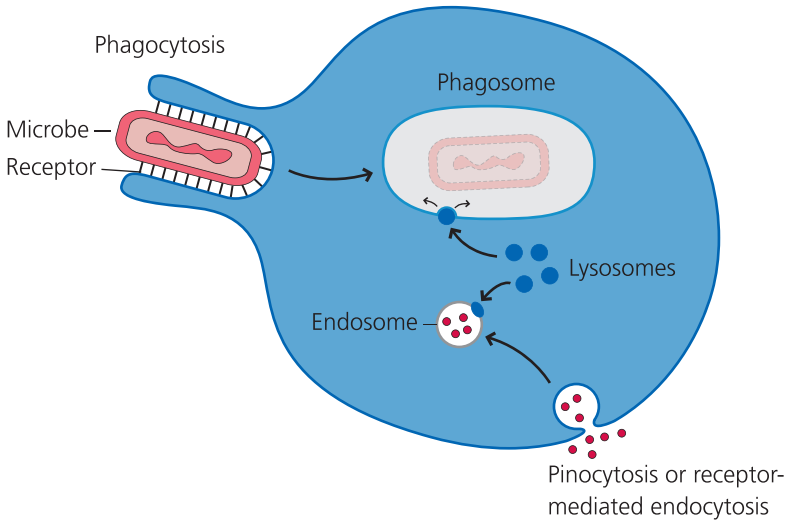

Fig. 1.9 Mechanisms of endocytosis. **Phagocytosis**. Phagocytes can internalize particles such as bacteria into vesicles called phagosomes. **Pinocytosis**. All cells engulf small quantities of fluids and their dissolved solutes. These are taken up in membrane-bound vesicles called (primary) endosomes. In all cases, the primary endosomes or phagosomes then fuse with other intracellular vesicles called lysosomes to form secondary endosomes or phagolysosomes in which the internalized contents can be degraded. This can lead to killing of phagocytosed microbes.

by internalizing small samples of fluid and solutes into membrane-bound vesicles called endosomes. This is the process of fluid-phase endocytosis or pinocytosis. It is used by cells, for example to obtain nutrients, and in some cases cell surface receptors extract the required nutrient molecules in a related process called receptor-mediated endocytosis. Some specialized cells are also capable of internalizing particles through the process of phagocytosis; the particles are contained in membrane-bound vesicles called phagosomes. In all forms of endocytosis, including phagocytosis, membrane-bound vesicles called lysosomes, containing catabolic enzymes, can fuse with the endocytic vesicle or the phagosome and release the enzymes into the vesicle. Generally speaking this usually leads to the degradation of the vesicular contents. Note that the term endocytosis can be used in a general sense to include phagocytosis (as we do), but is sometimes used for all processes other than phagocytosis. See Figure 1.9.

Phagocytes are specialized cells that are able to internalize particles such as bacteria and small protozoa, and are able to kill microbes intracellularly. The two main classes of phagocytes are macrophages and neutrophils. Other cells such as eosinophils are also weakly phagocytic, but this is not known to be one of their main purposes.

1.4.2.1 Macrophages

Macrophages reside in almost every tissue of the body and are important components of *both* innate and adaptive immune responses. Circulating precursors of macrophages, which are produced in the bone marrow, are called monocytes. When a monocyte enters a tissue it may develop into a form called mature macrophage.

Macrophages in tissues are generally long-lived cells (tattoos, which last for a lifetime, represent ink particles inside macrophages). Resident macrophages in connective tissues and solid organs play crucial roles in the remodelling and growth of organs during development and in regulation of normal tissue functions (homeostasis). Tissue-resident macrophages possess specialized receptors that recognize cells that have been programmed to die through the process of apoptosis and assist in tissue remodelling without scarring (e.g. during embryogenesis).

Infection most often begins in peripheral tissues and resident macrophages play very important roles in the initiation of innate immune response. They possess receptors (PRRs) that can recognize different types of infectious agent, enabling them to distinguish between broad classes of viruses, bacteria and fungi for example. Some of these receptors enable the macrophage to phagocytose the infectious agent so it can be destroyed intracellularly. Importantly, other PRRs signal to the nucleus to change gene expression, leading, for example, to the secretion of small, hormone-like proteins (cytokines; below) which act on other cell types. Crucially, some of the cytokines that resident macrophages secrete early in infection (as alarm signals; Section 1.2.3.1) then help to stimulate local inflammation by modifying the structure and function of the endothelial cells of blood vessels. Later they may also stimulate more distant tissues, inducing systemic inflammatory responses. See Figure 1.10.

Once the inflammatory process has been initiated, large numbers of monocytes can be recruited from the blood to the site of infection. These cells develop into inflammatory macrophages with a much larger repertoire of functions than the resident cells. (Depending on how they are being studied these cells are sometimes also called elicited macrophages.) For example, they are much more phagocytic and secrete an enormous diversity of molecules that help to amplify the inflammatory response, bring in other types of effector cells to the area and eliminate the infectious agent. These and other macrophages may also contribute to the repair and healing of the tissue.

In some circumstances macrophages can acquire new and highly potent antimicrobial killing mechanisms. This is particularly the case once the later adaptive immune responses have been initiated, although it can happen earlier. A key macrophage-activating agent, produced in such responses is

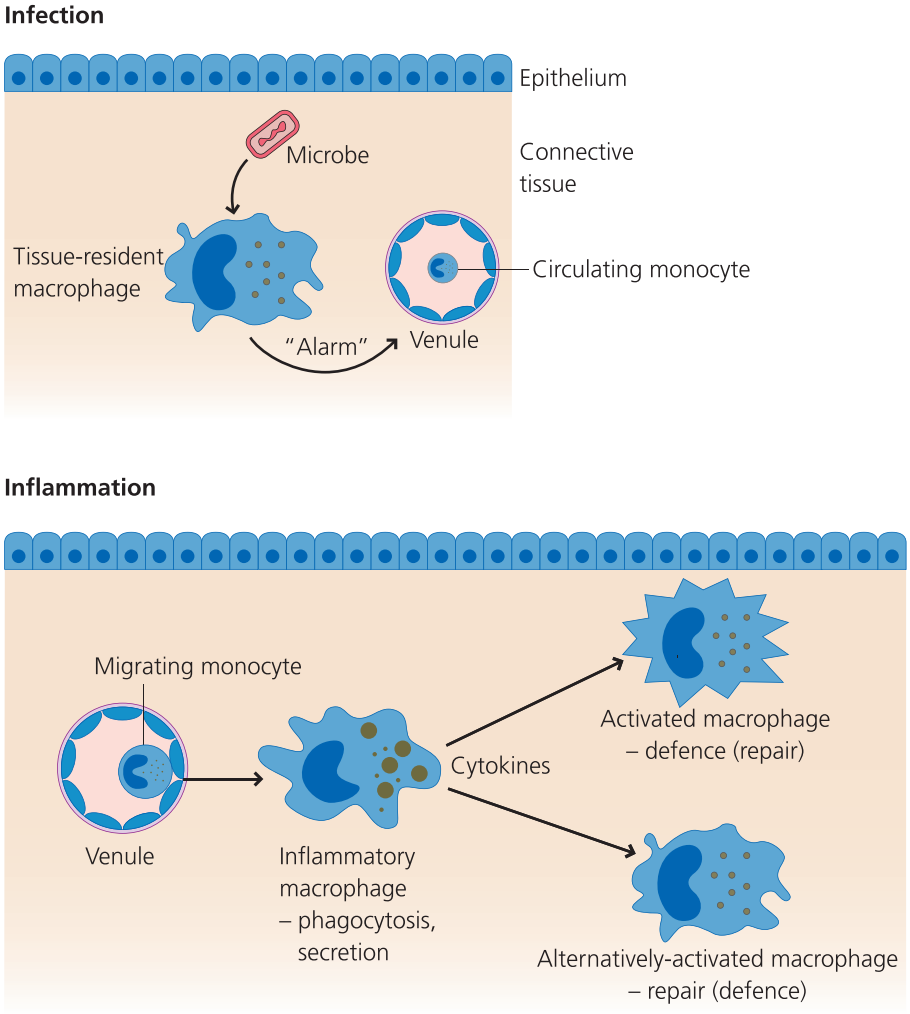

Fig. 1.10 Types of macrophages. Macrophages are plastic cells that can develop different specialized functions. **Tissue-resident macrophages** are long-lived cells present in connective tissues. In the steady state they are involved in homeostasis, helping to maintain the architecture of the tissue, and can also sense infectious agents and help to trigger inflammation (e.g. Figure 1.3). **Inflammatory macrophages**. Local inflammation recruits blood monocytes into tissues. In response to infectious agents these can become highly secretory cells that produce many innate effectors such as complement components. **Activated macrophages**. Innate and adaptive responses can help turn macrophages into potent anti-microbial cells. **Alternatively activated macrophages**. Macrophages can also develop functions involved in wound repair and healing, and may help to dampen down the inflammation.

the cytokine interferon (IFN)-γ. Activated macrophages do not have the ability to produce the wide variety of different mediators typical of elicited macrophages, but they concentrate on killing the microbes they have phagocytosed. For this they produce, for example, nutrient-depleting molecules that prevent growth and replication of the microbes, highly toxic agents that poison them, including reactive oxygen intermediates/species (ROIs/ROS), and a diversity of enzymes that digest them. Activated macrophages are very important in defence against certain bacteria, such as the mycobacteria, some of which cause tuberculosis and leprosy. In other circumstances different types of macrophage activation (e.g. alternative activation) or deactivation can be triggered, perhaps as sequential stages, depending on the local environmental conditions (e.g. which cytokines are present). You can see that the macrophage is therefore a highly adaptable cell type.

1.4.2.2 Neutrophils

Neutrophils are the most abundant leukocytes in human blood, comprising approximately 70% of total white blood cells. Neutrophils are crucial in defence against pyogenic (pus-forming) bacteria such as *Staphylococcus* and *Streptococcus* which typically cause abscesses and similar infections involving acute inflammation. Neutrophils are released from the bone marrow as mature cells and have very short lifespans (1–2 days). They are not present in normal tissues, but are rapidly recruited to sites of acute inflammation.

Neutrophils are highly phagocytic. They constitutively possess a wide variety of antimicrobial killing mechanisms (in contrast to macrophages, in which these are usually induced). Many of the molecules needed to generate killing mechanisms are preformed and stored in different types of cytoplasmic granules. When a microbe has been phagocytosed, some of these granules fuse with the phagosome, delivering their toxic contents – some of which are similar to those of activated macrophages (e.g. ROIs) – onto the microbe. Neutrophils may also have the capacity to kill microbes extracellularly. In addition to their anti-microbial agents the granules also contain proteolytic enzymes that breakdown (liquefy) the surrounding tissue. When neutrophils encounter bacteria that are able to resist killing, they die and in some infections, typically with *Staphylococcus aureus*, the liquefied tissues form the pus that discharges from abscesses. See Figure 1.11.

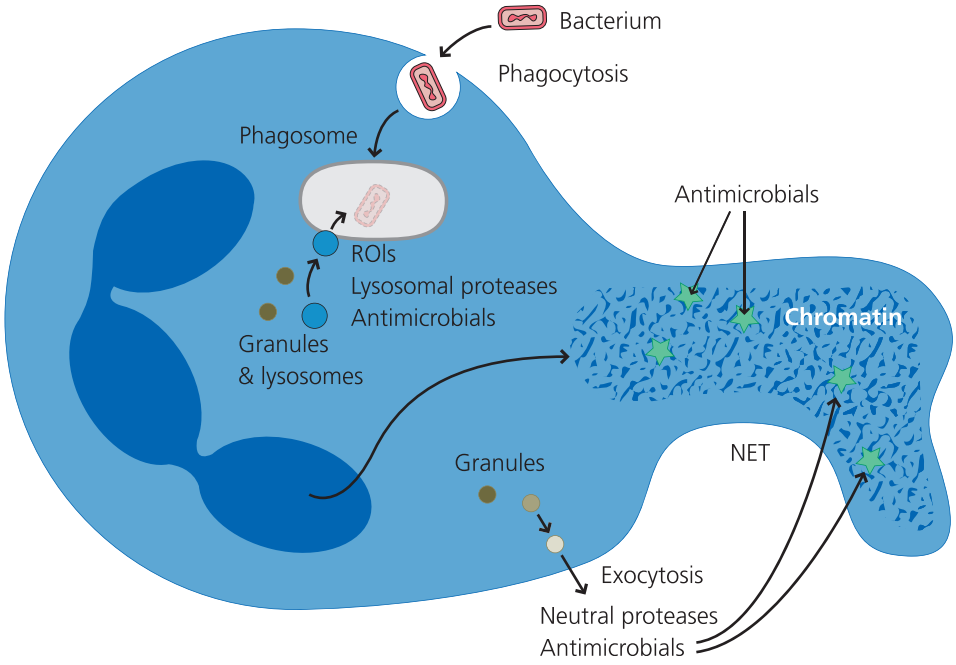

Fig. 1.11 Killing by neutrophils. Neutrophils can kill microbes intracellularly and perhaps extracellularly. **Intracellular killing**. After phagocytosis of microbes the phagosomes fuse with cytoplasmic granules that contain or can produce anti-microbial agents. The latter include reactive oxygen intermediates and other compounds that may be toxic to the microbes and proteases which may degrade them. **Extracellular killing**. These cells can also extrude **neutrophil extracellular traps (NETs)** composed of chromatin that are thought to trap extracellular microbes. The contents of other granules may subsequently discharge to release anti-microbial agents and proteases to help kill them, although this is not yet proven.

1.4.3 Mast Cells, Eosinophils and Basophils

As for the different phagocytes (Section 1.4.2), the functions of mast cells, eosinophils and basophils significantly overlap, although each, too, has its own specialized properties. Mast cells can be viewed as being resident cells in tissues, whereas the basophils and eosinophils are typically recruited to inflammatory sites. They are commonly found in the anatomical barriers of the body e.g. immediately under mucosal epithelia or in the skin.

1.4.3.1 Mast Cells

Mast cells are resident cells in mucosal tissues and loose connective tissues. They function, at least in part, by sensing infection or tissue damage and then triggering inflammation. Mast cells possess cytoplasmic granules that contain histamine and cytokines. Mast cells may be activated through their PRRs and by small molecules such as complement fragments. When activated these cells very rapidly release their stored mediators, but also synthesize cytokines and lipid mediators. These secreted molecules are generally involved in the induction of acute inflammation. The lipid mediators also induce contraction of smooth muscle, such as in the lung and airways and in the gut. In the latter case, muscle contraction may help expel parasites. Mast cells are, however, better known for the roles they play in pathological, allergic responses. See Figure 1.12.

1.4.3.2 Eosinophils

These granulocytes, normally representing 1–3% of all blood leukocytes, usually possess a bi-lobed nucleus and large cytoplasmic granules of different types that stain orange with the

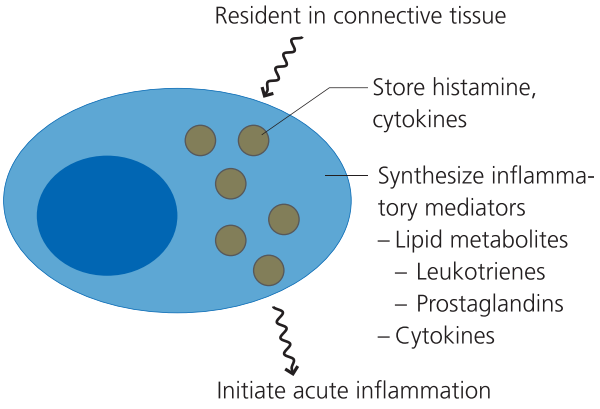

Fig. 1.12 Mediators produced by mast cells. Mast cells are present in all connective tissues. Mast cells have large cytoplasmic granules that store pre-formed inflammatory mediators such as histamine and cytokines, and which are discharged when the mast cell is activated (degranulation). Activated mast cells also synthesize inflammatory mediators including lipid metabolites and other cytokines when activated. Mast cells can be activated by pathogen molecules or by molecules produced during acute inflammation. They can also be activated during allergic reactions such as hay fever.

acidic dye, eosin (hence their name). They are recruited to certain types of inflammatory sites, particularly those associated with parasitic infections and allergic responses. As for mast cells, the contents of their granules are released when eosinophils are activated by cytokines. Other mediators can be synthesized later. Several functions of eosinophils overlap with those of mast cells (above). These include inducing the increased production of mucus, which may help prevent attachment of infectious agents to the underlying epithelial cells. Eosinophils may have a role in healing certain types of tissue damage, such as that caused by intestinal infestation of worms. Thus, eosinophils may be important in defence against parasites such as intestinal worms. See Figure 1.13.

1.4.3.3 Basophils

Basophils possess bi-lobed nuclei and their large cytoplasmic granules stain dark blue with basic dyes (hence the name). Basophils circulate in the blood in very small numbers (normally less than 1% of leukocytes) and are normally absent from tissues. However, they can be recruited into inflammatory sites, typically together with eosinophils (above). They are functionally similar to mast cells, although there are some differences, and basophils are also potent stimulators of inflammation.

1.4.4 Natural Killer Cells

All viruses need to infect cells in order to replicate. To limit viral replication and the release of new virions, immune cells have evolved that can kill virally infected cells and perhaps some tumour cells. The ability of an immune cell to kill another cell in this way is termed cellular cytotoxicity and the cell that does the killing is generally referred to as a cytotoxic cell. Such cells kill by triggering a process called apoptosis in the cells they recognize. All cells have the potential to undergo apoptosis (e.g. during tissue remodelling) and some specialized cells of the immune system have evolved mechanisms to latch on to this process; they therefore kill by enforced suicide rather than murder of their targets. The advantage of triggering this form of cell death is that the contents of the dead and dying cell can be rapidly eliminated, usually without triggering inflammation. One type of cell that can do this, although it may not be its principal function in host defence, is the NK cell. natural killer (NK) cells were first recognized by their ability to kill tumour cells in culture as soon as they were isolated from blood. They are present in normal blood and organs such as spleen and liver, but other NK cells can be recruited to inflammatory sites. Owing to their spontaneous cytotoxic capacity, they were termed natural killer cells – as opposed to cytotoxic T cells (CTLs) that need to be activated before they can kill (Section 1.4.5.2).

NK cells resemble lymphocytes, but in their resting state they contain large cytoplasmic granules. These granules contain specialized molecules, including one called perforin that can insert into membranes of the target cell and polymerize to form pores that allow entry of other molecules (particularly specialized enzymes called granzymes) that can trigger death of the target cell. This may be important in defence against some viral infections (e.g. herpes viruses). As the molecules contained in granules are pre-formed, NK cells can kill very rapidly. NK cells additionally possess membrane molecules such as Fas ligand which binds to death-inducing Fas on target cells and can also trigger apoptosis. (In contrast, these components normally have to be induced over time in CTLs.) Crucially, NK cells additionally secrete a variety of cytokines that induce or regulate the activity of other immune cells. See Figure 1.14.

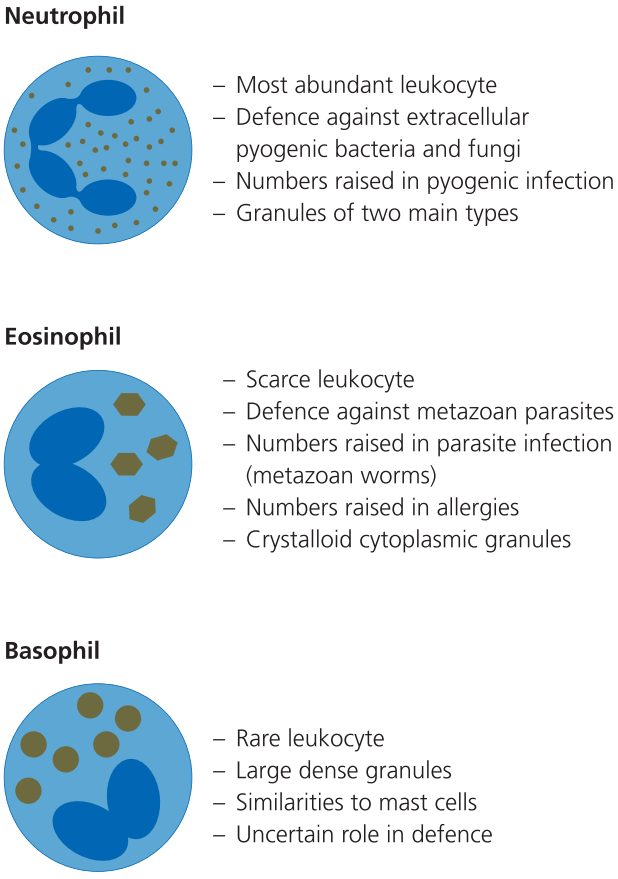

Fig. 1.13 Types of granulocytes. Granulocytes are leukocytes that contain different cytoplasmic granules with characteristic staining properties. All can be recruited to different sites of inflammation. **Neutrophils** are the most abundant leukocytes in blood. Large numbers can be recruited rapidly to sites of acute inflammation (Figure 1.6) and their production from the bone marrow can be greatly increased during some bacterial infections. They are highly active phagocytes (Figure 1.11). **Eosinophils** are normally present in low numbers, but can be recruited particularly into mucosal tissues. Larger numbers can be produced from the bone marrow during other types of infection, especially with large parasites against which they may provide resistance or defence, and in allergic responses such as asthma. **Basophils** are normally very rare in blood. They, too, can be recruited to inflammatory sites where they typically accompany eosinophils. They have very similar properties to mast cells but their roles in host defence are poorly understood.

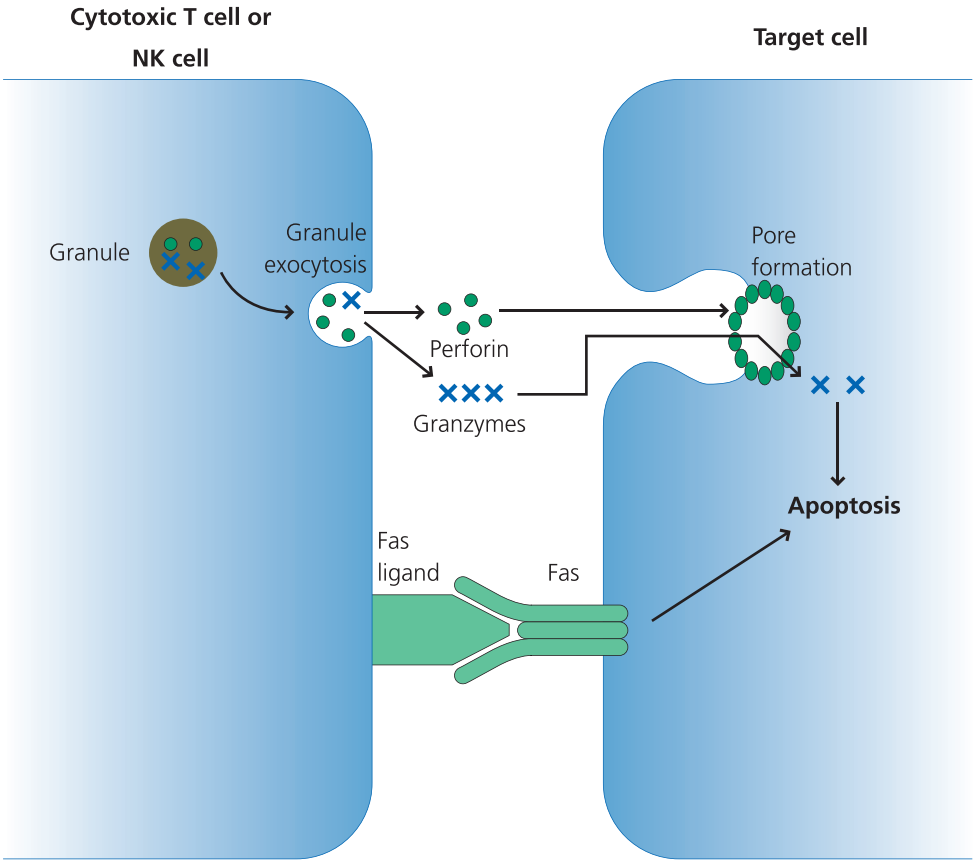

Fig. 1.14 Mechanisms of cellular cytotoxicity. NK cells and cytotoxic T cells can kill infected cells by inducing apoptosis in a process called cellular cytotoxicity. **Granule-dependent mechanisms**. Pre-existing (NK cells) or newly generated (CTLs) granules store molecules which can trigger apoptosis. These include perforin that can polymerize to form pores in target cell membranes and enables molecules such as granzymes to enter the cytosol where they trigger apoptosis. **Granule-independent mechanisms**. Cytotoxic T cells and NK cells can also express cell surface molecules such as Fas ligand which, when it bind to Fas on the target cell, initiates apoptosis in the target cell.

So how do NK cells recognize and kill their target cells? As we shall see later (Chapter 4) it turns out that NK cells possess a large set of specialized receptors that belong to different structural families and which are entirely different from PRRs or lymphocyte antigen receptors. Essentially, NK cells monitor the levels of specialized molecules that are present on other cells (particularly major histocompatibility complex (MHC) molecules; below). If these levels are normal, killing by the NK cells is inhibited by inhibitory receptors. However, if they are significantly reduced, typically because a virus has infected a cell, activating receptors can become engaged that overcome the repressed state and lead to killing by the NK cells. The ability of NK cells to kill other cells that lack (or have very low levels) of normal components was originally termed the missing self hypothesis.

1.4.5 Lymphocytes

Lymphocytes are the cells that mediate adaptive immunity. In the resting state they are inactive "naïve" precursor cells that need to be stimulated by antigen, and usually by other signals before they become fully activated. The mechanisms of activation are complex, but the dangers of inappropriate activation (e.g. leading to autoimmune diseases; Chapter 7) are so great that there need to many points at which activation can be regulated. Once it has been activated a lymphocyte can become an effector cell, which is usually short-lived, or a long-lived memory cell capable of being reactivated should an infection be reoccur.

In this section we will introduce two major classes of lymphocytes, and briefly describe their properties and functions. As noted earlier, these comprise the T cells – which are in fact of two main types, CD4 T cells and CD8 T cells – and the B cells. These are the "conventional" types of lymphocyte that play central roles in adaptive immunity. Conventional T cells are also called αβ T cells. There are in addition other types of less conventional (or "unconventional") lymphocytes, including γδ T cells and NKT cells (not to be confused with NK cells!) which are discussed in Chapters 5 and 6. See Figure 1.15.

1.4.5.1 CD4 Helper and Regulatory T Cells

CD4 T cells, which when activated become conventional helper T (T_h) cells or regulatory T (T_{reg}) cells, are one of the

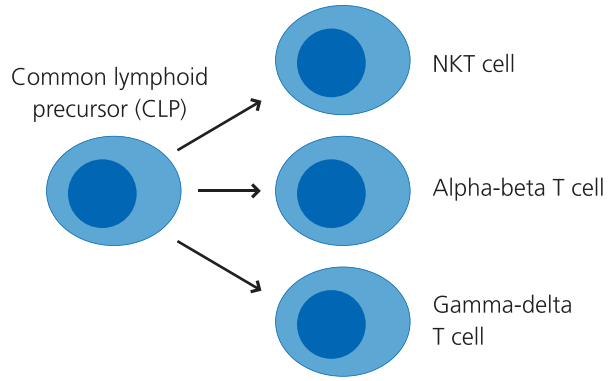

Fig. 1.15 Different types of T cells. αβ T cells. In humans and mice these are the predominant T cells. They express highly diversified antigen receptors (αβ TCR); they pass repeatedly through all secondary lymphoid tissues (recirculation). **γδ T cells**. In foetal mice, different waves of non-conventional T cells with much less diversified antigen receptors (γδ TCR) populate epithelia; they are produced before αβ T cells. **NKT cells**. These are very specialized T cells that represent another developmental pathway. Some **invariant NKT (iNKT)** cells express αβ TCR, but with very little diversity.

two main types of T cells. They are so-called because they possess a molecule called CD4 (in multiple copies, of course) that is involved in recognition of the cells with which they interact. As for all naïve lymphocytes, CD4 T cells circulate in the bloodstream and migrate through secondary lymphoid tissues. They are small, resting cells. To function, they need to be activated and in primary responses this occurs in the secondary lymphoid tissues. In secondary lymphoid tissues DCs (below) activate CD4 T cells and regulate their differentiation into cells capable of mediating different functions. These effector T cells then either interact with other cells locally within the secondary lymphoid tissues (e.g. they can help to activate B lymphocytes; below) or they migrate to peripheral sites of inflammation and infection and interact with different cell types.

There are at least four main ways in which CD4 T cells can be instructed to function, and the respective T cell subsets are termed T_h1, T_h2, T_h17 and T_{reg} cells. These subsets stimulate different types of adaptive immune response, either by recruiting or modifying the functions of the cells of innate immunity, initiating responses in other adaptive cells or by bringing in new cells and molecules into the response. See Figure 1.16.

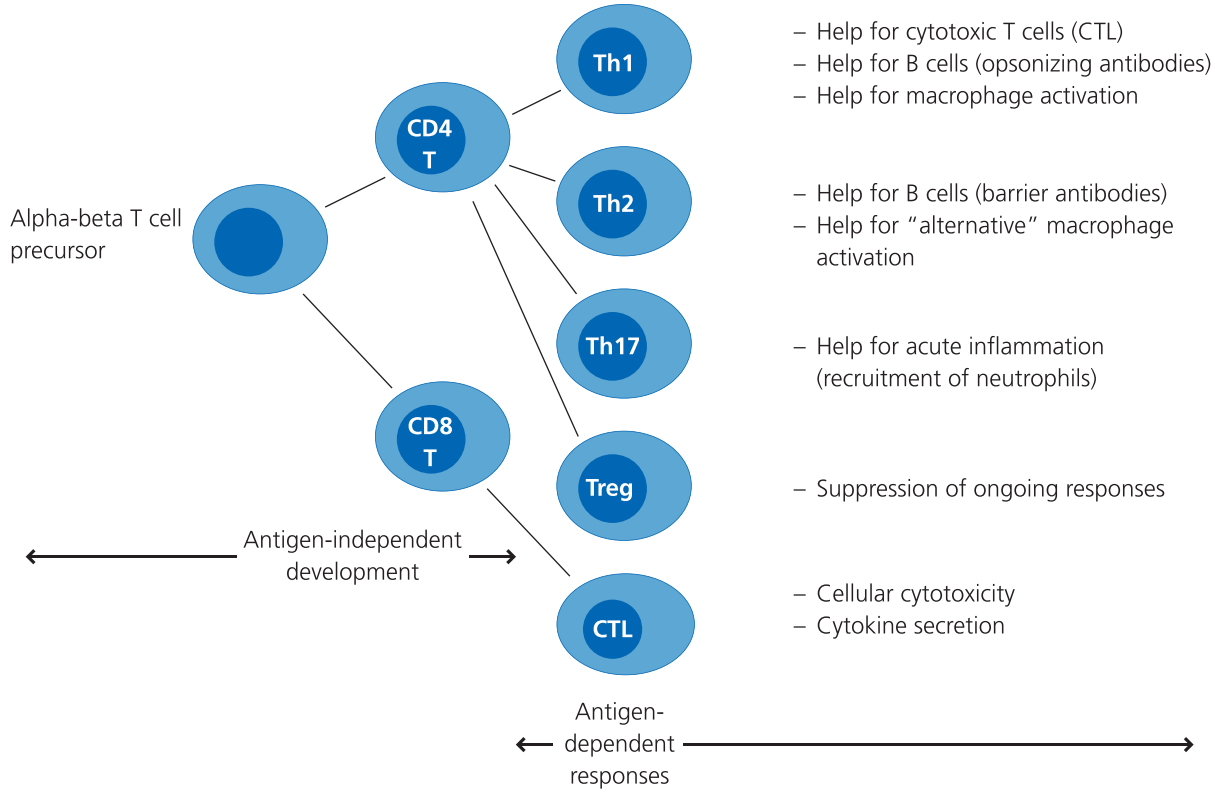

Fig. 1.16 Subsets of conventional αβ T cells. Two main αβ T cell subsets are produced in the thymus: CD4 and CD8 T cells. Each can acquire specialized (polarized) functions during immune responses. **CD4 T cells**. These may develop into T_h1, T_h2 or T_h17 cells depending on the type of infection. They regulate the functions of other cell types or help to recruit and orchestrate different effector mechanisms, some of which are indicated. CD4 T cells can also develop into T_{reg} cells that can suppress immune responses. **CD8 T cells**. These cells can develop into cytotoxic cells (CTLs) and may also adopt polarized functions somewhat resembling those of CD4 T cells although these are less well understood.

In general terms the functions of these activated CD4 T cells are as follows:

- T_h1 cells stimulate anti-microbicidal and cytotoxic effector functions of immunity (e.g. they activate macrophages and recruit and activate cytotoxic cells, both NK cells and CD8 T lymphocytes). They also instruct B cells to develop into plasma cells and secrete certain types of antibodies (which are of different classes, Section 1.5.5.3) that can interact with some of these cells. T_h1 responses may be particularly important for later defence against some types of bacterial and viral infections (e.g. tuberculosis, influenza).
- T_h2 cells stimulate the barrier functions of immunity (e.g. they recruit and maintain eosinophils, cause macrophages to become alternatively activated, and induce the production by plasma cells of other types of antibodies that can interact with these cells; Section 1.5.5.3). This type of response may be particularly important for host defence or resistance against parasitic infections such as worm infestations
- T_h17 cells are particularly efficient at recruiting neutrophils to the site of infection; hence, neutrophils (like other innate cells) can be recruited in both the innate and adaptive responses of immunity. This type of response may be particularly important for defence against other types of bacteria, particularly bacteria that cause acute inflammation such as *Staphylococcus* and *Streptococcus*, and perhaps some fungi.
- T_{reg} cells suppress the responses of other cells, including DCs and/or other lymphocytes. This type of response may be particularly important in switching off immune responses when an infectious agent has been eliminated and in ensuring that harmful responses are not made against innocuous agents (including components of the body itself).

These are probably the best understood subsets, although there are in fact other types of CD4 T cells with specialized functions that are noted in Chapter 5.

1.4.5.2 CD8 T cells

CD8 T cells represent the other main type of conventional T cell (see Figure 1.16). These T cells possess multiple copies of a molecule called CD8 that is involved in recognition of the cells with which they interact. Following activation, these T cells can become cytotoxic T cells capable of inducing apoptosis in cells they recognize (note, in contrast, that NK cells do not need to be activated before they can be cytotoxic; above). CD8 T cells, like CD4 T cells, circulate in the bloodstream and migrate through secondary lymphoid tissues. To function they also need to be activated and this occurs in the secondary lymphoid tissues. When CD8 T cells are fully activated, they become cells with potent cytotoxic activity. These cells leave the secondary lymphoid tissues, and enter peripheral sites of inflammation and infection. Here they can kill virally infected cells. They do so in two main ways – through perforin and granzymes, and through Fas ligand–Fas interactions (which are very similar to those used by NK cells).

As cytotoxic cells, CD8 T cells are a central component of adaptive immunity to viruses such as the influenza virus. However, they can also produce cytokines that (i) are directly toxic, such as tumour necrosis factor (TNF)-α, which induces apoptosis by binding to death-inducing receptors on other cells, or (ii) can modulate or enhance the functions of innate cells (e.g. IFN-γ, the major macrophage-activating cytokine), thus providing additional mechanisms by which they may help to eliminate infectious agents. Note that polarized subsets of cytokine-secreting CD8 T cells have also been postulated and named in accordance with CD4 T cell subsets (T_c1, T_c2, etc.).

1.4.5.3 B Lymphocytes

B lymphocytes are also small, resting cells, morphologically indistinguishable from T cells. When they are appropriately activated their primary function is to develop into plasma cells, which can be regarded as antibody-synthesizing factories, or to become memory cells. In many cases B cells need help from T cells to become activated and to develop into plasma cells, and the T cells also control the type of antibody that they make (see Figure 1.16). This type of response, which is typically made in response to protein antigens by B cells in specialized sites of secondary lymphoid tissues (termed follicles), is therefore termed a T-dependent (TD) response. However, there are different types of B cells. Another subset of B cells, located in a specialized site of the spleen (called the marginal zone) can produce antibodies to other types of antigen, such as polymeric carbohydrates, without needing any help from T cells and this is an example of a T-independent (TI) response. Finally, a different type of non-conventional B cell (called B-1 cells in the mouse) can produce so-called natural antibodies in the apparent absence of any antigenic stimulation. The functions of different types of antibody are described in detail in Chapter 6. See Figure 1.17.

1.4.5.4 Memory Lymphocytes

A central feature of adaptive immunity is the phenomenon of immunological memory. This is a crucial property of lymphocytes and a function of adaptive immune responses in general. As we mentioned earlier, once an initial infection has been overcome by a primary adaptive immune response, a long-lasting state of resistance to re-infection by the same organism ("immunity") can often be achieved. Good examples are immunity to childhood infections such as measles, and the long-lasting immunity that can be induced by vaccination against smallpox and tetanus. Immunity in these cases may last for many years and is due to the development, in the course of the adaptive response, of populations of memory lymphocytes, both T and B cells.

Once an infectious agent has been cleared, most of the expanded populations of effector T cells, or plasma cells, die. However, populations of antigen-specific memory T cells, both CD4 and/or CD8 T cells, and memory B cells persist.

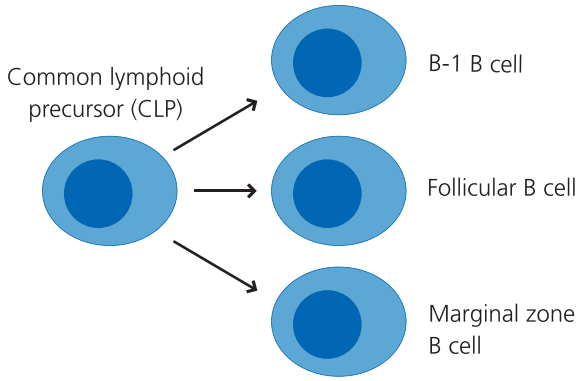

Fig. 1.17 Different types of B cells. Different types of B cell develop during foetal and neonatal life (*cf.* Figure 1.15 for T cells). All can develop into plasma cells and make antibodies. They may respond to different types of antigen. **Follicular B cells**. The predominant, conventional, B cells in humans and mice have highly diversified antigen receptors (BCRs) and pass repeatedly through all secondary lymphoid tissues (recirculation). **B-1 cells**. In mice, non-conventional B cells with much less diversified BCRs populate the peritoneal and pleural cavities; they are first produced before conventional B cells. **Marginal zone B cells**. These are sessile cells in splenic marginal zone that represent an alternative pathway of development to follicular B cells.

The numbers of these antigen-specific clones of lymphocytes are now higher than before the infection occurred and memory cells can be more rapidly reactivated if the infectious agent is encountered again. Hence, secondary responses are much larger and more rapid, and usually lead to highly efficient clearance of the infectious agent. See Figure 1.18.

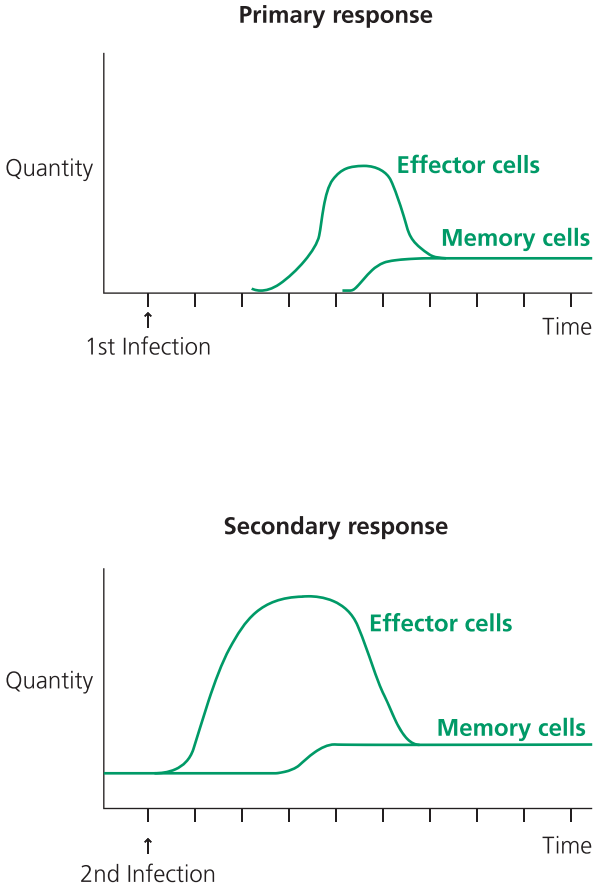

Fig. 1.18 Effector and memory lymphocyte responses. **Primary responses**. In response to a new infection, effector lymphocytes are produced after a lag (when the cells are being activated and expanded) and their numbers slowly decrease as the microbe is cleared. A population of memory lymphocytes then appears and persists, often for a lifetime. **Secondary responses**. If the same infection occurs again, memory lymphocytes can rapidly develop into effector cells and help to clear the infection more efficiently. They then revert back to memory cells (or are replaced by new ones) and can respond again similarly if the infection happens at any time in the future. These principles apply for both T cell and B cell responses. The efficiency of secondary responses is seen even more clearly in antibody responses, since more appropriate types of antibodies of higher affinity can be produced, compared to those secreted in a primary response (not shown; see Chapter 6.)

1.4.6 Dendritic Cells (DCs)

There are different types of DCs and their nomenclature can be confusing. We will focus primarily on "classical" DCs whose primary function is to trigger and regulate most types of adaptive immune responses, particularly the responses of CD4 T cells. Such DCs, which are transiently resident in peripheral tissues sense different types of infectious agents using the PRRs that are also expressed by innate immune cells. They can also internalize infectious agents (viruses, bacteria, etc.) or smaller antigens derived from them (e.g. bacterial toxins, components of parasites). See Figure 1.19.

Depending on the particular type of infection that has occurred, and in response to other stimuli such as the particular cytokines that are produced in inflammatory sites, these DCs then change their properties. They migrate in increased numbers from peripheral tissues into secondary lymphoid tissues (e.g. from the skin into the lymph nodes that drain that site), transporting the antigens they acquired in peripheral sites of infection in forms that can be recognized by T cells, i.e. peptide-MHC complexes. In these lymphoid organs the DCs can interact with antigen-specific T lymphocytes, particularly CD4 T cells, and, because they now express specialized molecules that are needed for full activation of naïve T cells (a process called costimulation), they can initiate many types of adaptive immune responses. Depending on the type of infection, DCs also cause activated CD4 T cells to adopt specific functions appropriate to the type of microbe that needs to be eliminated. Having done their job, DCs die in secondary lymphoid tissues.

Plasmacytoid DCs (pDCs) are a different cell type. They are called plasmacytoid because they possess much rough endoplasmic reticulum and, in this respect, they resemble plasma

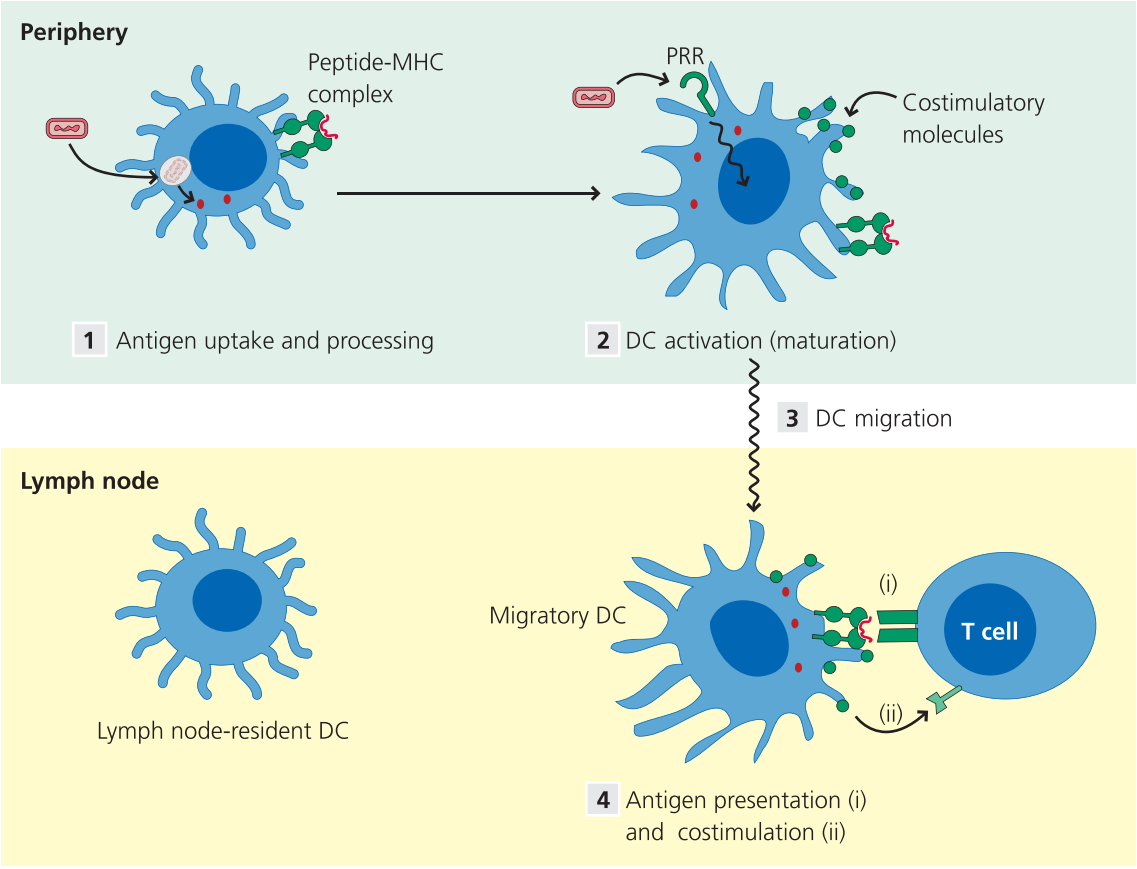

Fig. 1.19 Functions of "classical" dendritic cells. Classical DCs are found in nearly all peripheral tissues; in skin epidermis they are called **Langerhans cells**. (1) When infection occurs, these cells internalize and degrade microbial antigens to forms that can be recognized by T cells (peptide–MHC complexes). (2) Sensing of the pathogen through PRRs also causes them to increase expression of specialized costimulatory molecules that are needed to activate T cells. (3) They then migrate into secondary lymphoid tissues (e.g. from skin to draining lymph nodes via afferent lymph). (4) These migratory DCs can now activate antigen-specific T cells, triggering adaptive immunity. Lymph nodes additionally contain a distinct population of resident DCs that play less understood roles in T cell activation or regulation than the migratory DCs.

cells. They are very potent secretors of cytokines collectively called type I IFN and may play a role in anti-viral defence. When stimulated via PRRs they rapidly secrete a variety of pro-inflammatory cytokines which probably also play a role in the regulation of T cell activation, but their real functions in immune responses are still unclear.

Finally, there is another cell type called the follicular DC (FDC) that we discuss in other chapters. Despite their name, these are a totally different type of cell that must not be confused with either classical DCs or pDCs. FDCs are localized in specialized sites of secondary lymphoid organs (the follicles) where they play central roles in B cell responses, as opposed to the several types of classical DCs that are involved in T cell responses (above).

1.4.7 Coordination of Immune Responses

To conclude this section on the cellular basis of immunity, we will summarize a few key principles.

As a first general rule, the type of innate or adaptive response that occurs after infection is tailored to the type of infectious agent that initiated it. Thus, the immune system generates an immune response that is most appropriate for eliminating the infectious agent. For example, we have seen above that phagocytes are involved in direct killing of bacteria, cytotoxic cells can kill cells that have been infected by viruses, and eosinophils and basophils may help in resistance to worm infestations. Each of these cell types uses very different mechanisms to perform its functions.

A second general rule is that cells that are involved in any immune response do not act independently, they are regulated by, and can regulate the functions of, other cells. The production of innate cells from the bone marrow may be increased or decreased during both innate and adaptive responses, their accumulation at sites of infection is regulated by inflammation and, importantly, their functions can be modulated. In this way each cell can help to fine tune the type of immune response that needs to be induced at different times after infection.

It is a third general rule that all immune responses need to be initiated, particularly in response to infection, and that the overall response needs to be properly coordinated and regulated. Just as very different types of response can occur in innate immunity, the same is true for adaptive responses. In adaptive immunity, specialized cells are required to trigger lymphocyte responses and a specialized set of lymphocytes then controls the overall type of response that follows. The most important controlling cells are DCs, and CD4 T cells that have helper or regulatory functions. Together these cells are responsible, with assistance from other cell types, for co-ordinating the adaptive immune response. (To use a business analogy, DCs might be viewed as the executives, CD4 T cells as middle management and all the other cell types we have mentioned as the workers. To a significant extent DCs assess the risk, take strategic decisions and tell the CD4 T cells what to do; in turn, CD4 T cells instruct the different types of worker to help achieve the task.)

Finally, of course, nothing could happen without molecules. Some key molecules of immunity are considered in the next section.

1.5 Molecular Basis of Immunity

The primary function of the immune system is to eliminate infectious agents that have breached the natural defences. This is brought about by the integrated actions of different cells and molecules that, directly or indirectly, lead to their elimination. Having outlined the cells of immunity, we now examine the molecular basis of immunity. We describe in a little more detail some of the molecules mentioned above, and introduce others that also play key roles in immunity.

1.5.1 Cell-Associated and Soluble Molecules of Immunity

Some of the most important classes of molecules expressed by immune cells are those with the following functions:

i) Controlling the positioning of immune cells within the body; for example, they enable these cells to localize within normal tissues or to reach the sites of infection.
ii) Enabling the recognition of infectious agents and other signals, so that the cell can make an appropriate response.
iii) Communicating with other cells in the vicinity or in more distant tissues, to help bring about a coordinated response.
iv) Directly or indirectly acting as effector molecules; for example, by helping to kill the infectious agent (inside or outside of cells) or to kill the cells that may harbour infectious agents (cellular cytotoxicity).

In addition, many cell-associated molecules, which include receptors for soluble molecules, are linked to intracellular signalling cascades that frequently lead to changes in gene expression or other cellular functions that are needed in specific responses.

Many molecules involved in immunity belong to different superfamilies in which there is a common underlying structure, although functions of the family members may differ widely. For example, molecules of the immunoglobulin superfamily contain different numbers of so-called immunoglobulin domains possessing a characteristic structure. For the purposes of this introduction we will, however, use *function* to group the molecules of immunity into six main types (Figure 1.20):

- **Adhesion molecules** which, for example, enable leukocytes to interact with endothelial cells during migration out of the blood into specific sites, components of connective tissues such as the extracellular matrix, and other cells.
- **Innate agonist receptors**, particularly PRRs that activate the innate immune system.
- **Antigen receptors** which enable lymphocytes to recognize infectious agents or to detect the presence of infectious agents inside other cells.
- **Cytokines** which enable cells to signal to other immune and tissue cells in the same vicinity or at a distance; a subset of these are called chemokines that are involved in directing the migration of cells (e.g. to sites of infection).
- **Effector molecules** that directly kill the infectious agent or enable it to be targeted to specific cells for elimination.
- **Intracellular signalling molecules** without which immune cells (or, indeed, any other cell type) would be unable to function.

1.5.2 Adhesion Molecules

In all cases, cells that enter tissues from the blood must cross the barrier of endothelial cells that line blood vessels and enter extravascular sites. This process is called extravasation or transendothelial migration. Clearly, any cell needs to discriminate between one site and another (e.g. peripheral versus secondary lymphoid tissues, or normal versus inflamed tissues). Cells also need to able to migrate within tissues and to retain their positions in these tissues. These functions are dependent on adhesion molecules.

The selective homing of different cells to different sites at different times is controlled by a remarkable recognition system. In part, this involves adhesion molecules of leukocytes, which are of two main classes: selectins and integrins. These bind to counter-ligands on endothelial cells that are collectively termed vascular addressins because, together, they provide "addresses" to help leukocytes find their way through and into different types of tissue. A third set of molecules involved in cell homing are not adhesion molecules, but are receptors for a specialized set of cytokines called chemokines (below).

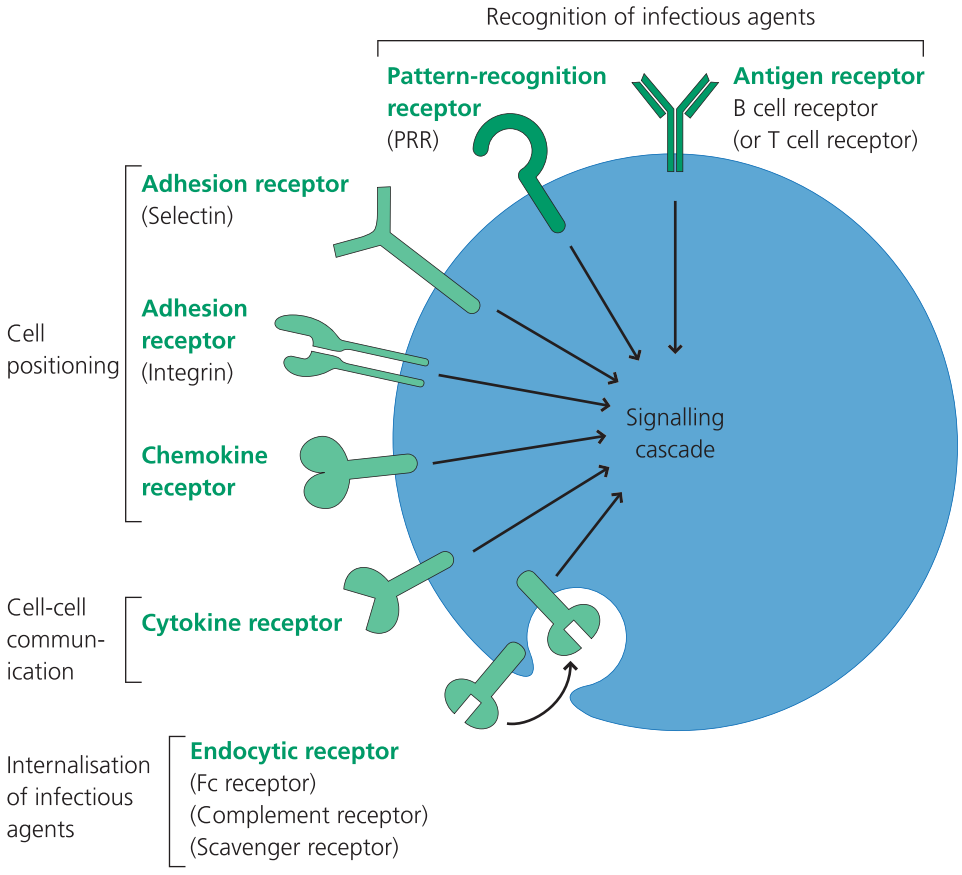

Fig. 1.20 Examples of molecules involved in immune responses. Recognition of infectious agents. PRRs are expressed by many different types of cell, particularly innate cells, and enable them to recognize different classes of infectious agent. Antigen receptors (TCRs and BCRs) are expressed only by lymphocytes and enable them to recognize specific components of infectious agents. **Endocytic receptors**. These facilitate uptake of molecules and particles which are sometimes coated with other immune components (e.g. antibodies or complement). **Communication molecules**. Cytokine receptors bind cytokines that are produced by the same or other cells and change cellular functions. Some cytokines, called chemokines, generally alter cell migration after binding to chemokine receptors. **Cell-positioning molecules**. These are needed for cells to migrate to and from normal or inflamed tissues, or to adhere to and communicate with other cells. **Signalling molecules**. Binding of ligands to receptors typically triggers biochemical cascades within the cell involving intracellular signalling molecules. These form pathways that ultimately change the behaviour of the cell (e.g. movement) or change gene expression so the cell can acquire new roles in immunity.

Collectively, the permutations and combinations of different selectins, integrins. chemokines and chemokine receptors provides a highly discriminatory system to ensure that the right cells go to the right places at the right time – a system that one might term the "post code" (or "ZIP code") principle. See Figure 1.21.

1.5.2.1 Selectins

Leukocytes in the blood can transiently attach to and roll along the endothelium of venules. Rolling is usually mediated by selectins (lectins are proteins that bind to carbohydrate ligands). Rolling gives the cell time to interact with molecules expressed on the endothelial surface that define the type of endothelium, and hence to identify the tissue in which it finds itself (e.g. skin or gut) and the state of that tissue (e.g. normal or inflamed). These complementary molecules, which are constitutively expressed or inducible at different sites, contain carbohydrate residues that can act as ligands for the selectins.

1.5.2.2 Chemokines and Chemokine Receptors

Chemokines are a specialized class of cytokines (Section 1.5.4) that can stimulate cells to migrate directionally along a concentration gradient of the chemokine. Directed cellular migration is called chemotaxis. Chemokines can be produced in tissues by many different types of cell (e.g. by macrophages and mast cells in response to infection). As well as promoting directional cell migration within the tissues where they are produced, chemokines may be transferred across the endothelium to the luminal (blood) side and become attached to the endothelial cells. Different types of leukocytes such as

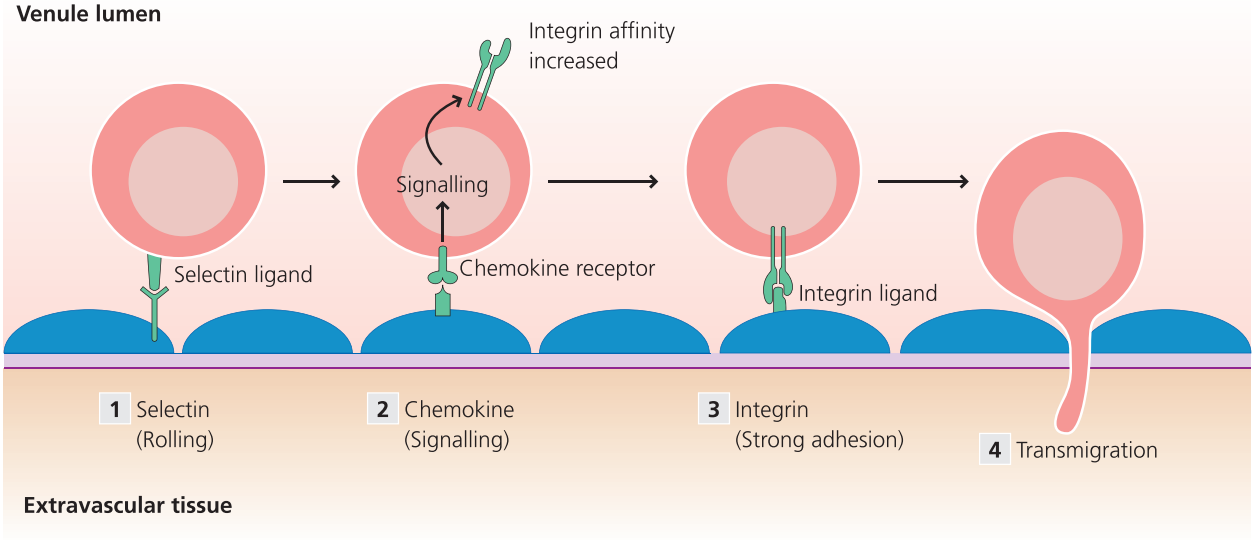

Fig. 1.21 The "post code" principle for leukocyte extravasation. Leukocytes from blood must enter specific tissues and organs (extravasation) to mount immune responses during infection (peripheral tissues in innate responses and secondary lymphoid tissues in adaptive responses). The combination of different types of molecule expressed by vascular endothelial cells resembles a post code (ZIP code) that can be read by the leukocyte. **(1) Selectins**. Selectins, through weak binding to their carbohydrate ligands, mediate transient attachment and rolling of leukocytes along the endothelium. **(2) Chemokine receptors**. Chemokines produced at sites of inflammation are transported across the endothelium to the luminal side where they are displayed for recognition by leukocytes with corresponding receptors. **(3) Integrins**. Intracellular signalling from chemokine receptors leads to activation of integrins, which can now bind strongly to counter-receptors on the endothelial cells, leading to firm attachment. **(4) Molecules involved in transmigration**. Other types of molecule (not shown) enable the leukocyte to cross between or directly through the endothelial cells to enter extravascular tissues.

neutrophils, or later in the response activated T cells, possess different types of chemokine receptors. The corresponding chemokines, which are attached to the endothelial cells, bind to chemokine receptors and, in turn, activate some of the integrins on the leukocyte. Once activated, integrins bind very strongly to their ligands (below).

1.5.2.3 Integrins

When leukocytes receive appropriate signals via chemokines they stop rolling and attach firmly to the endothelial cells. The rolling of leukocytes can be arrested because of the strong binding that occurs between the integrins and their counter-ligands on the endothelium. Integrins exist in two states either high or low affinity. The integrins of circulating leukocytes are in the low-affinity state and incapable of strong binding. The switch to the high-affinity state occurs in response to the leukocyte receiving signals through its chemokine receptors.

Once within the tissue, different integrins can also enable the cell to attach to components of the extracellular matrix and, later, to the cells with which they may need to physically interact during the immune response. Within the tissue, a gradient of chemotactic molecules – including chemokines produced at the site of infection – is established. These permit the directional migration of the leukocyte towards the site of infection itself. Other types of integrin are not involved in migration but have different functions.

1.5.3 PRRs and Antigen Receptors

All immune responses, both innate and adaptive, are initiated by recognition of molecules, and particularly components of infectious agents. Some components may act as agonists in innate immunity, while others are recognized as antigens by the lymphocytes of adaptive immunity. We will highlight the functions of four different types of cell-associated recognition systems in the immune system.

- PRRs play central roles in the initiation and regulation of innate immunity, and in part regulate adaptive responses.
- BCRs on the surface of B cells can recognize antigens directly; after a B cell develops into a plasma cell, BCRs can be secreted as antibodies. Other molecules are involved in signalling from BCRs to the B cell when antigen recognition occurs, while others regulate B cell activation and responses.
- TCRs of T cells remain cell-associated and are not secreted. TCRs *cannot* recognize antigen directly. Instead the antigen (usually a peptide) must be bound to a MHC molecule. As for B cells, other molecules are additionally involved in T cell activation and responses.
- MHC molecules bind peptides and enable conventional T cells to recognize antigens.

1.5.3.1 Pattern Recognition Receptors (PRRs)

PRRs are widely distributed on immune and other cells. Other types exist in soluble forms and are sometimes termed pattern recognition molecules (PRMs). A key feature of PRRs is that they are generally involved in responses to components of infectious agents that are not synthesized by their host (e.g. humans). Some PRRs may also be involved in responses to components of the host itself, but which are usually only produced in times of damage or stress as during an infection. PRRs are phylogenetically ancient and are also present in invertebrates. One of the best understood types of PRRs, the Toll-like receptors (TLRs) were first discovered in insects.

Cell-associated PRRs are present in different cellular compartments, on the cell surface, in endosomes or in the cytosol. As such they have the potential to recognize (directly or indirectly via an associated molecule) infectious agents that are present outside the cell, have been internalized (e.g. by phagocytosis in macrophages) or have infected cells. The outcome of recognition by PRRs differs depending on the cell type that is involved. The best understood PRR functions are those involved in innate immunity, the induction of inflammation and the initiation of adaptive immunity. Thus, PRRs expressed by phagocytes can promote phagocytosis or stimulate the production of cytokines that induce inflammation (below) whereas. PRRs expressed by mast cells may lead to the release of their granule contents. Whereas PRRs expressed by DCs stimulate cellular responses, including the secretion of cytokines, which help to regulate T cell responses. See Figure 1.22.

PRRs are also expressed on epithelial cells, leading to secretion of anti-microbial agents; endothelial cells, helping to regulate the recruitment of different types of leukocyte in inflammatory responses; and even on lymphocytes, where their functions are not fully understood.

1.5.3.2 B Cell Receptors (BCRs)

B lymphocytes have evolved to recognize components of infectious agents that are derived from the extracellular compartments of the body, including the tissue fluids. These infectious agents include, for example, free viruses and bacteria in the blood or extracellular fluid. This recognition is initially mediated by membrane-bound BCRs. BCRs have evolved to recognize complementary parts of the three-dimensional structure of foreign antigens, such as part of a molecule on the surface of a virus or bacterium – these are termed conformational epitopes. The same is true when BCRs are secreted as antibodies (below). The only difference between a BCR and its corresponding antibody is whether or not it contains a small molecular portion that attaches it to the cell membrane, and sometimes an additional component that can help the soluble molecule polymerize into dimers or pentamers.

Generation of Diversity of Lymphocyte Antigen Receptors A vast number of antigen receptors of different structures – and hence of different antigen specificities – can be assembled during early development of B cells in the bone marrow, and of T cells in the thymus (below). In general, each B cell possesses multiple copies of BCRs of only one specificity; the same applies for T cells. The process of generating the repertoires of lymphocyte antigen receptors occurs through a remarkable process of diversification that is not known to occur in any other cell type. Unlike all other genes in the genome, those that encode lymphocyte antigen receptors exist in germline DNA not as functional genes, but as gene segments. To create a functional antigen receptor gene, these segments are rearranged at the DNA level in lymphocytes. In humans and mice this process occurs by a genetic mechanism termed somatic recombination.

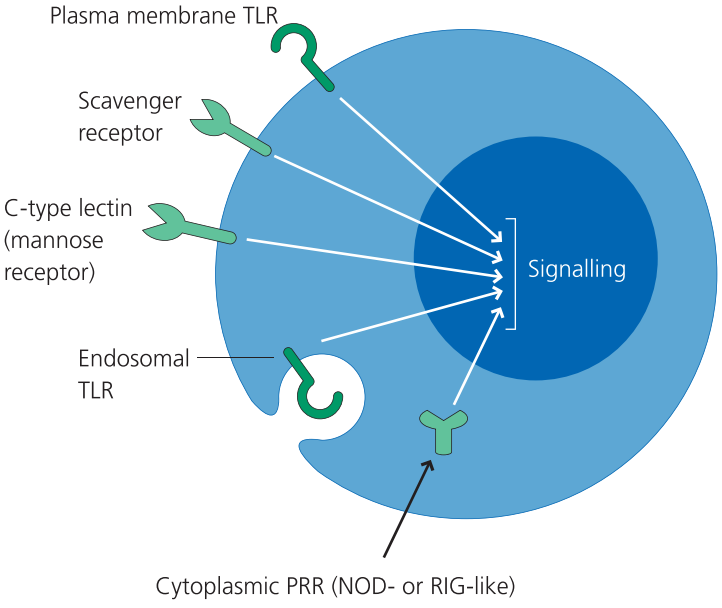

Fig. 1.22 Types and locations of pattern recognition receptors. PRRs are localized in different cellular compartments. Widely expressed components of different classes of infectious agent act as agonists for different PRRs and stimulate different cellular responses (e.g. phagocytosis, degranulation, cytokine secretion). **Plasma membrane PRRs.** These PRRs include some TLRs, C-type lectin receptors and scavenger receptors. Typically they are involved responses to bacteria, fungi or protozoa. **Endosomal PRRs.** Some TLRs are expressed on endosomal membranes. Typically they respond to nucleic acids (RNA, DNA) from viruses and bacteria. **Cytoplasmic PRRs.** These include RNA helicases, which for example recognize nucleic acids of viruses, and NOD-like receptors which recognize components of bacteria that may have escaped into the cytoplasm. Many PRRs signal to the nucleus to change gene expression, but others modulate other cell functions by acting on cytoplasmic components (such as actin, leading to changes in cell shape (not shown).

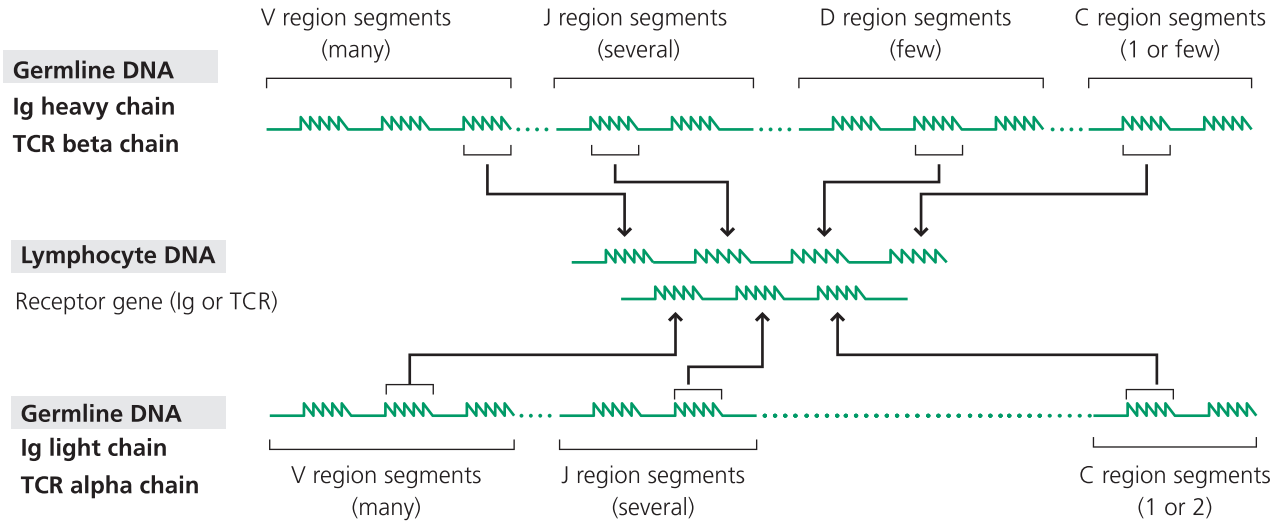

Fig. 1.23 Rearrangement of antigen receptor genes. BCRs and TCRs are comprised of two different molecules – immunoglobulin (Ig) heavy (H) and light (L) chains, and TCR α and β chains respectively. Each chain consists of variable and constant regions. Each chain is encoded in a particular region (locus) of a different chromosome but, in germline DNA, the receptor genes are not present as functional genes. In lymphocytes, functional antigen receptor genes are assembled by rearrangement of gene segments. **IgH and TCR β genes**. There are three groups of gene *segments*: V, D and J in the variable region locus. Largely at random, one D segment joins to one J segment and the DJ segment then joins to a V segment. This encodes the variable (V) *region* of the IgH chain or the TCR β chain respectively. **IgL and TCR α genes**. A similar principle applies but D segments are absent. One V segment joins to one J segment, and the assembled VJ segment encodes the V region of the IgL chain or the TCR a chain. **C (constant) region segments**. Downstream of the V, D and/or J segments, there are one or more C region segments. The newly assembled VDJ or VJ segments become juxtaposed to the closest C region segment and a functional gene is created. In the case of the IgH locus there are several different C regions enabling different types of BCR to be assembled with the same V region; these can be secreted as antibodies with different corresponding functions but with the same antigen specificity.

In their membrane-bound form, attached to B cells, BCRs are composed of two pairs of molecules, termed heavy (H) chains and light (L) chains. These associate to form a "Y"-shaped molecule (e.g. Figure 1.24). The top two regions of the "Y" – called the variable regions – are responsible for antigen recognition. Each of these is formed from a variable region of a H chain combined with the variable region of a L chain and, together, these determine the antigen specificity of the molecule. The stem of the Y – called the constant region – is attached to the cell in a BCR. It also controls all aspects of the biological and immunological functions of the corresponding antibody when it is secreted. These molecules are encoded by the immunoglobulin genes that are formed after DNA rearrangement of the corresponding segments.

To make a variable domain of a BCR, different DNA segments are recombined. These are called V, D and J segments for H chains, and V and J segments for L chains. There are multiple V, D and J segments, and joining happens largely at random, but selecting only one of each. Where the joins are made, specialized mechanisms can introduce further variations in the DNA, thus changing the structure of the V region gene that is produced and hence the antigenic specificity of the molecule it encodes. Very similar process are involved in generation of TCRs (below). For BCRs, the assembled variable region genes are then attached to one of a few constant region genes that encode part of the constant region of the antibody. Depending on which C region gene is used, a different type or class of antibody is produced. Assembly of a functional BCR is crucial for B cell development – if a functional BCR is not produced, the developing cell dies; the same is true for T cells (below). See Figure 1.23.

Functions of BCRs When they are first produced, B cells are small, resting cells. These mature, but naïve (antigen-inexperienced), B cells are not able to do much by themselves. To develop into plasma cells that secrete antibodies, or to develop into memory B cells, they first need to be activated. Recognition of antigen by the BCR is important for B cell activation. BCRs on the surface of B cells are associated with a molecular complex, CD79, that delivers signals to the B cell when antigen recognition occurs and helps to activate the B cells. Another important function of BCRs is to trigger internalization and degradation of the antigens they recognize. These antigens are subsequently presented at the cell surface (as peptides bound to MHC molecules; below) to enable recognition by specific T cells that can then instruct the B cells what to do next, particularly in the case of antibody responses against protein antigens. See Figure 1.24.

However, regulation of lymphocyte responses is, in general, a tightly controlled process that depends in part on what has happened (or still is happening) in the innate response. If, for example, complement has been activated, one particular complement component (bound to an antigen) can bind to a receptor

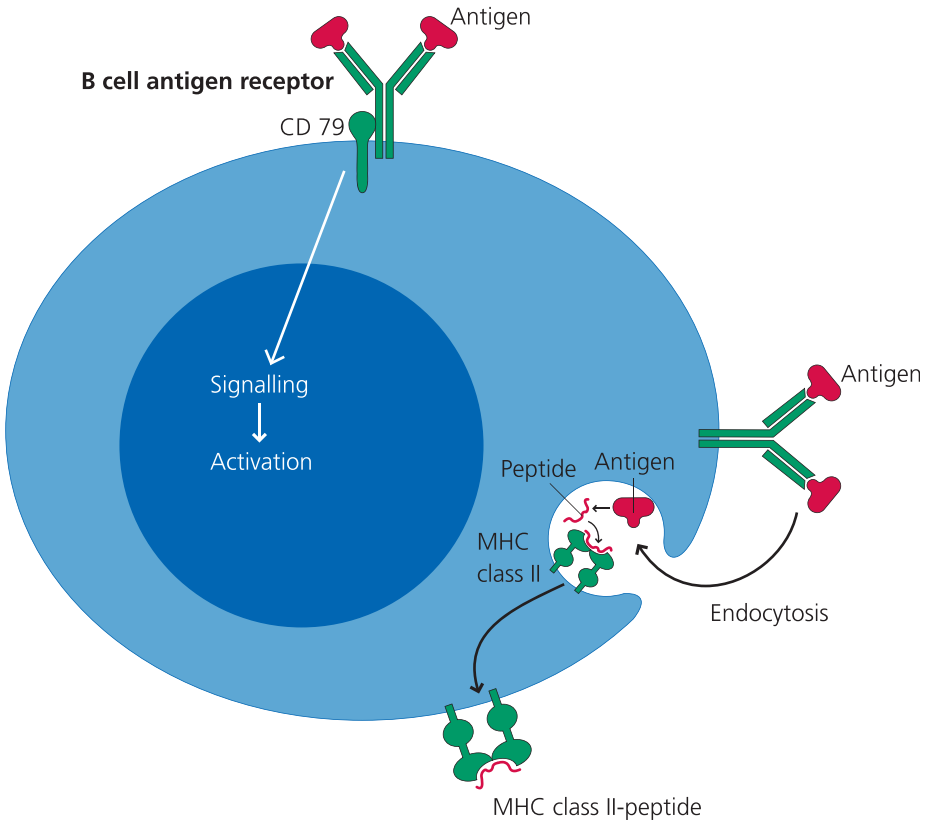

Fig. 1.24 Functions of B cell antigen receptors. All B cells express membrane-bound BCRs. **Antigen recognition**. BCRs recognize structural features on antigens known as conformational determinants or B cell epitopes. These are three-dimensional surfaces of folded microbial proteins, carbohydrates or glycolipids, for example. **Intracellular signalling**. BCRs are associated with a molecular complex, CD79, which triggers intracellular signalling following antigen recognition. These signals can help to activate a naïve B cell, after which it may develop into a plasma cell that secretes its BCRs as antibodies. **Antigen internalization**. Antigens bound to BCRs can be internalized and degraded. Peptides from protein antigens can be expressed as peptide–MHC complexes at the cell surface, enabling T cells to recognize the B cells and change their functions (e.g. to instruct them to make different types of antibodies).

complex (CD19/CD21/CD81) on the surface of B cells and deliver powerful signals to increase B cell activation. Other B cell molecules, such as CD40 and CD40 ligand, are involved during communication with activated CD4 T cells, which in many adaptive responses help to instruct the B cells as to what type of antibody they should secrete. See Figure 1.26.

During antigen-specific responses of B cells, further changes can be introduced into their immunoglobulin genes. First, B cells can change the constant domains of their BCRs and antibodies. A new constant region gene (attached to the pre-assembled variable region genes) may be selected to produce a different type (or class) of antibody with a different function (Section 1.5.5.3). This is called class switching. Second, B cells can also change the variable domain of their BCRs and antibodies. This is because mutations can be introduced into the variable region genes in a process called somatic hypermutation. Potentially this can increase the strength of recognition (affinity) of the BCR and of the respective antibodies that can be produced when the B cell develops into a plasma cell. The general increase in average affinity of antibodies that is seen after repeated antigenic stimulation is called affinity maturation and is a direct consequence of somatic hypermutation. It is important to stress that class switching and somatic hypermutation do *not* occur in TCRs.

1.5.3.3 T Cell Receptors (TCRs)

In contrast to B cells, T cells have evolved to recognize other cells that may *contain* foreign antigens. These include, for example, specialized cells such as phagocytes that have internalized bacteria or cells that have been infected by viruses. This recognition is mediated by membrane-bound TCRs. There are two different types of TCRs and the two main populations of T cells that express them generally have very different functions. The TCRs of conventional T cells in humans and mice are composed of a pair of molecules called the **α chains** and **β chains**, which combine to form an αβ TCR; these T cells are therefore also called αβ T cells. (Remember there are other types of T cells, but these are discussed in Chapter 5.) Conventional αβ TCRs have evolved to recognize peptide–MHC complexes on the surface of other cells. See Figure 1.25.

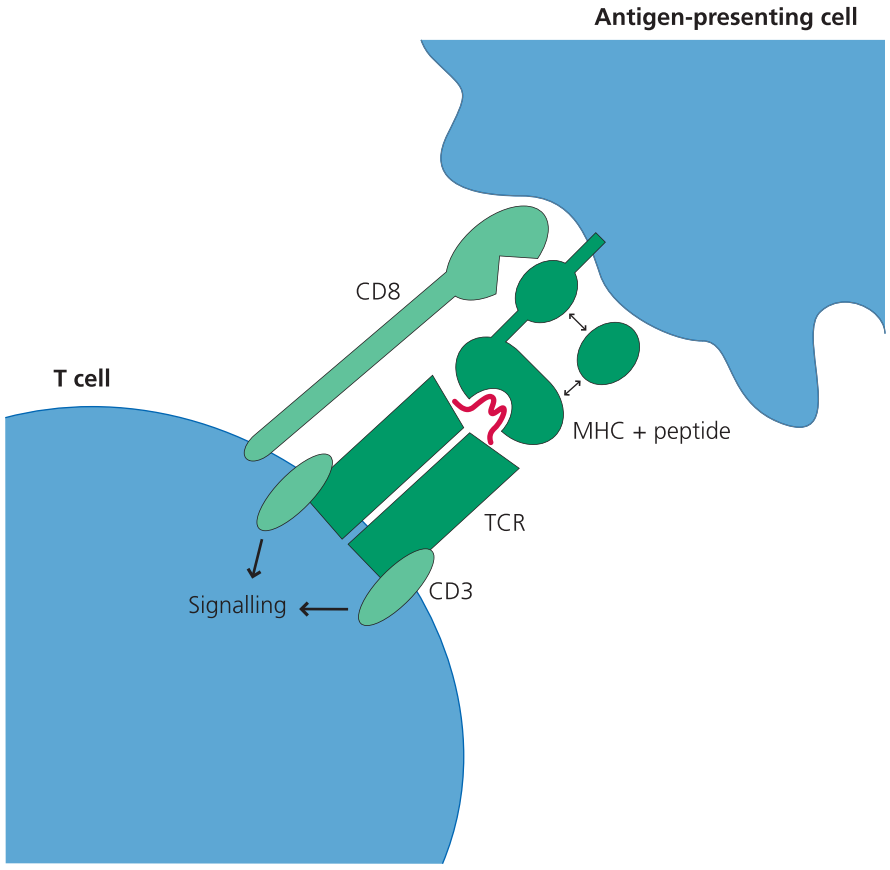

Fig. 1.25 Structure and function of T cell receptors. Conventional T cells express plasma membrane αβ TCRs; these are structurally related to immunoglobulin molecules, but functionally very different. **Antigen recognition**. αβ TCRs do not recognize whole proteins. Small peptides are produced by degradation of microbial proteins present in different cellular components. These peptides then bind to MHC molecules that transport them to the cell surface. Conventional αβ TCRs can then recognize these peptide–MHC complexes (but not either alone). The peptide represents a sequential determinant or (in association with an MHC molecule) a T cell epitope. **Intracellular signalling**. TCRs are associated with a molecular complex, CD3, which triggers intracellular signalling when TCR recognition occurs. These signals, to which CD8 molecules (or CD4 molecules; not shown) also contribute, represent signal 1 that is necessary for T cell responses to occur, but which is usually not alone sufficient for naïve T cells to become activated.

A vast number of αβ TCRs of different structures, and hence antigenic specificities, can potentially be assembled during development of T cells in the thymus. However, as for BCRs, these differ only in the variable antigen recognition domain at the top of the molecule, while the stem remains essentially constant. In general, every T cell can be thought of as having multiple copies of TCRs of only one specificity. TCR genes are generated through DNA rearrangement in a manner highly analogous to that described for BCR genes (above) – involving V, D and J segments for the β chain, and V and J segments for the α chain. However, the rearranged TCR variable region effectively associates with only one type of C region gene that cannot produce a secretory protein. Hence, the TCR of T cells is always membrane-bound (it cannot be secreted like antibodies) and T cells cannot undergo class switching (they keep the same TCR for life). In addition, mutations cannot be introduced in TCR variable regions, so T cells cannot undergo somatic hypermutation, and affinity maturation during T cell responses does not occur.

Functions of Co-Receptors on T Cells As we have seen there are two main subsets of conventional αβ T cells; CD4 and CD8 T cells. It is impossible to discriminate between the two subsets of T cells on the basis of the TCRs that they express. However, these subsets have very different functions. As already described in Section 1.4.5, CD8 T cells can develop into cytotoxic cells that can kill cells containing foreign antigens (e.g. virally infected cells). In contrast, CD4 T cells secrete a variety of cytokines and act as helper or regulatory cells by interacting with other cell types. For example, as noted above, CD4 T cells can provide help to B cells, particularly during responses to protein antigens, and can also regulate the functions of other cells such as macrophages. It is the expression of CD4 or CD8 that differentiates the different subsets of T cells. These molecules help the T cells to distinguish between cells containing different types and origins of antigen (see MHC; below) and also deliver signals to the T cells which help to trigger T cell activation.

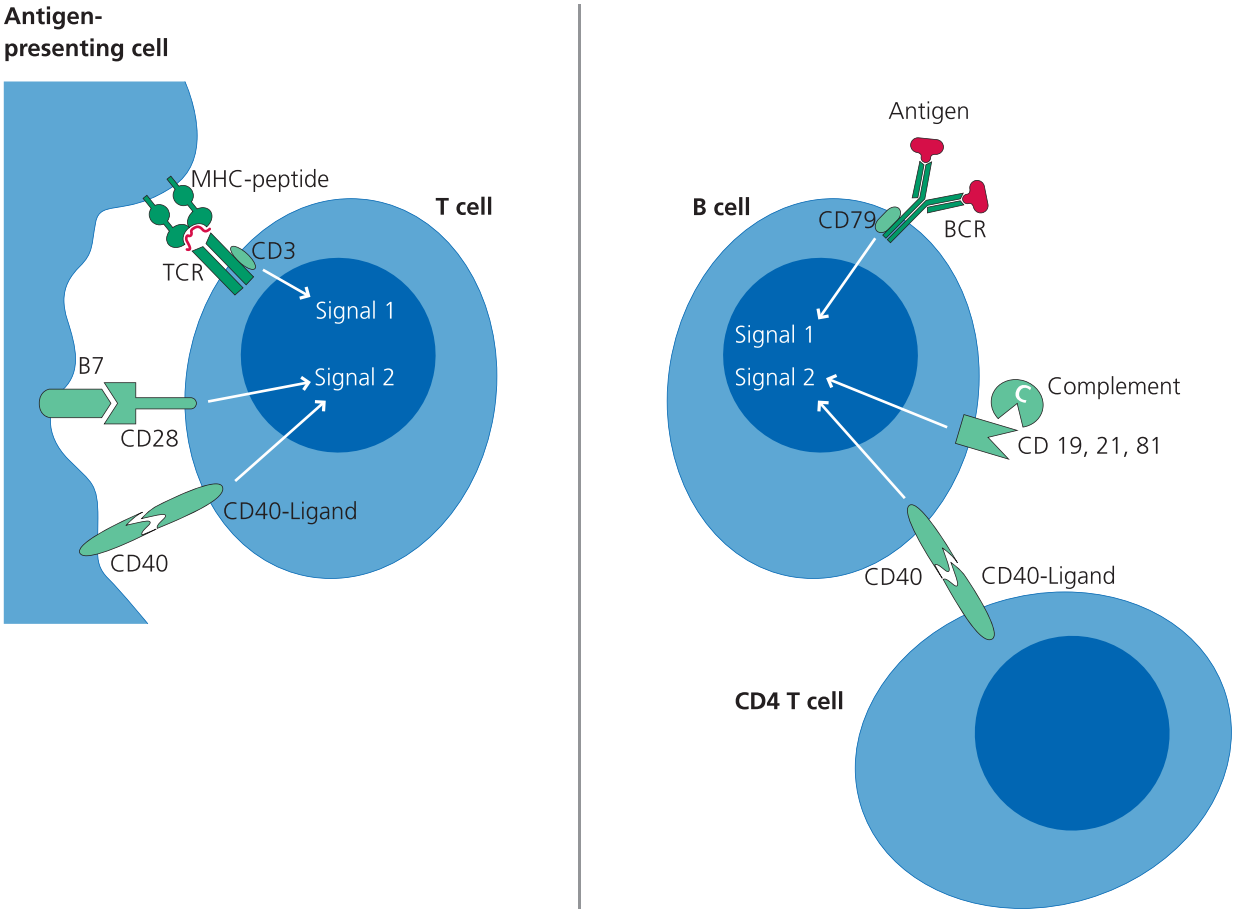

Fig. 1.26 Costimulation of lymphocytes. For naïve T and B cells, antigen recognition through TCRs and BCRs respectively (Signal 1), is not normally sufficient to induce full activation. Instead, they need additional signals (Signal 2) to provide costimulation. For **T cells** the most important are provided when B7 molecules (CD80, 86), typically expressed by activated DCs, bind to CD28 on T cells; additional signals can be provided by CD40 and CD40 ligand interactions. For **B cells**, binding of CD40 ligand on activated CD4 T cells to CD40 on the B cell is one of the most important for production of antibodies against protein antigens; other signals that are delivered when an activated complement component binds to a complex containing CD19 greatly enhance B cell responses. Cells that do not receive sufficient costimulation do not undergo full activation and may become unresponsive (anergy) or die. This can result in antigen-specific unresponsiveness and tolerance.

Functions of TCRs and Costimulatory Molecules To develop into the different types of T_h or T_{reg} cells, or into cytotoxic cells, naïve T cells first need to be activated. Recognition of antigen by the TCR is essential for T cell activation. TCRs on the surface of T cells are associated with another molecular complex called CD3 (compare CD79 on B cells; above) that delivers signals to the T cell when recognition occurs and helps to activate the T cells. This alone, however, is insufficient to fully activate a naïve T cell. In addition to the TCR–CD3 complex, T cells also possess molecules that deliver additional, crucial, activating signals to the cell when recognition occurs. When these interact with complementary molecules on other cells, particularly DCs that have been stimulated by infectious agents, T cell activation can occur. These molecules are termed costimulatory molecules. Examples of these include some members of the B7 family of molecules, which interacts with CD28 on T cells, and CD40 and CD40 ligand. Both antigen recognition *and* costimulation are needed for initial T cell activation; this principle generally also applies for B cell activation. A most important point to remember is that once a T cell has been activated, it no longer needs costimulation and can make a response when it recognizes any other cell containing antigen. The same is true for some memory T cells. See Figure 1.26.

1.5.3.4 Major Histocompatibility Complex (MHC) Molecules

Antigen recognition by B cells can occur directly, because their BCRs have evolved to recognize antigens *outside* cells (e.g. components derived from viruses or bacteria in the tissue fluids). However, antigen recognition by T cells *cannot* occur directly, because the antigens for which TCR are specific are *inside* other cells (e.g. a virus in the cytosol of an infected cell or a bacterium in the phagosome of a macrophage).

If recognition of antigen by T cells cannot occur directly, it is necessary for any cell containing antigen to "show" it, or "present" it, to the T cells instead. This is the function of the classical MHC molecules which are expressed by almost every cell of the body. The function of these MHC molecules is to

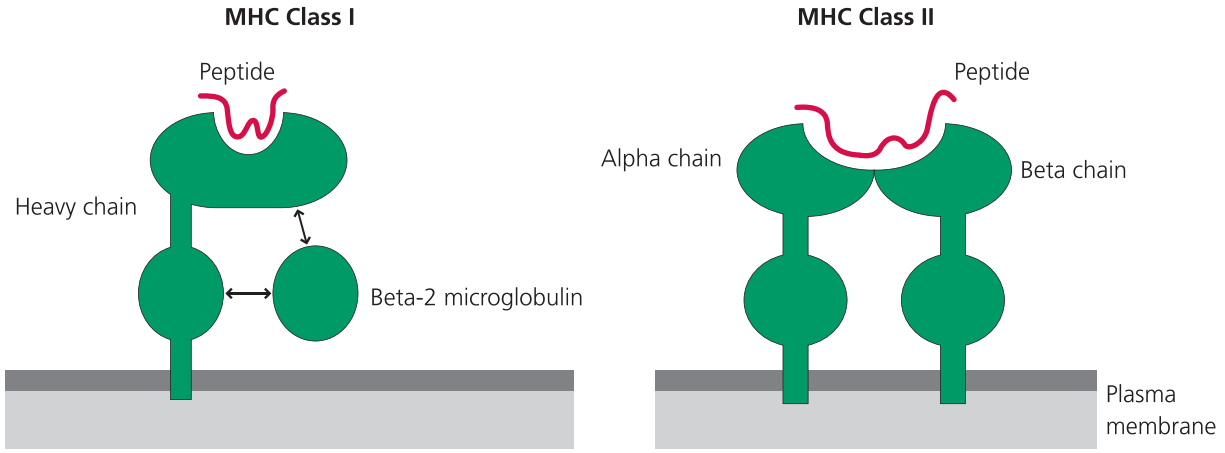

Fig. 1.27 Types of classical MHC molecules. Classical MHC molecules bind peptides and these complexes are recognized by "conventional" αβ T cells. **MHC class I molecules** contain a heavy chain, non-covalently associated with an invariant molecule, β_2-microglobulin. In contrast, **MHC class II molecules** are heterodimers composed of α and β chains (not to be confused with the molecules that comprise the TCRs). Both types of classical MHC molecules contain an antigen-binding groove that can potentially bind many different peptides (one at a time). They are also highly polymorphic, differing from each other mostly in the amino acid residues that form the antigen-binding groove which thus determine the precise nature of the peptides that can be bound.

bind representative samples (usually peptides) of molecules (usually proteins) that are synthesized within a cell, or which have been internalized by the cell, and to transport them to the cell surface. (So called non-classical MHC molecules have different functions as discussed in Chapter 5.) One molecule of peptide can bind to one classical MHC molecule. Every cell is able to degrade proteins that it synthesizes within the cytoplasm, while a more limited number of cells (e.g. macrophages) can degrade proteins that have been internalized in phagosomes. If these samples (generally, small peptides) happen to be derived from "foreign" infectious agents, complexes of foreign peptides and MHC molecules are displayed at the cell surface. In turn, αβ TCRs can bind to these foreign peptide–MHC complexes, thus permitting the T cells to recognize antigens that are present inside cells.

There are two different types of classical MHC molecules; MHC class I and MHC class II. During their biosynthesis MHC class I and II molecules are routed through different cellular compartments. Hence, they can bind peptides derived from different sites. As a general rule MHC class I molecules, which are widely expressed on different cell types, bind peptides that have been produced within the cytoplasm (e.g. where viruses often infect and replicate). In contrast MHC class II molecules, which are expressed on a more limited number of cell types, bind peptides that have been produced within endosomes or phagosomes (e.g. where pathogens can be internalized). See Figure 1.27.

MHC Molecules and T Cell Recognition How do the different subsets of CD4 and CD8 T cells discriminate between the different MHC molecules and bound peptides? The answer is quite simple and very elegant. CD8 T cells use the CD8 molecule (in conjunction with their TCR) to recognize peptide–MHC class I complexes. Any cell containing foreign antigen in the cytosol can therefore potentially be killed by CD8 T cells after they develop into CTLs. In contrast CD4 T cells, which can develop into T_h1 or T_h2 cells for example, use the CD4 molecule (in conjunction with their TCRs) to recognize peptide–MHC class II complexes. Any cell expressing MHC class II that contains foreign antigen in endosomes or phagosomes can therefore be recognized and its functions can be modulated by the CD4 T cells. See Figure 1.28.

Function of MHC Molecules in Presenting Antigens T cell-mediated immunity is crucial in defence against infection, and the ability of MHC molecules to bind and present peptides from infectious agents to T cells is essential for T cell activation and thus for host defence in general. Infectious agents are usually multiplying very rapidly, generating mutants, and any mutation that modifies a peptide so that it cannot bind to a MHC molecule will give the agent a selective advantage by facilitating evasion of the immune response. Since we cannot mutate our MHC molecules fast enough to keep up with the high rate of mutations in many microbes, we need other ways to maintain the efficacy of our MHC molecules in defence against infection.

How is this efficacy ensured? First, MHC molecules are highly promiscuous peptide receptors: one MHC molecule can potentially bind thousands of possible peptides (although one at a time). Thus, a few MHC molecules can cover a very large number of pathogen-derived peptides, increasing the chances that a given pathogen might be recognized by the respective antigen-specific T cells. However, the possibilities are not unlimited, so any given MHC molecule may not be able to bind a certain peptide. Second however, any individual expresses multiple MHC molecules and these are co-dominantly expressed. This means that the cells of any individual express a set of MHC molecules from both maternal and paternal chromosomes, thus increasing the number of

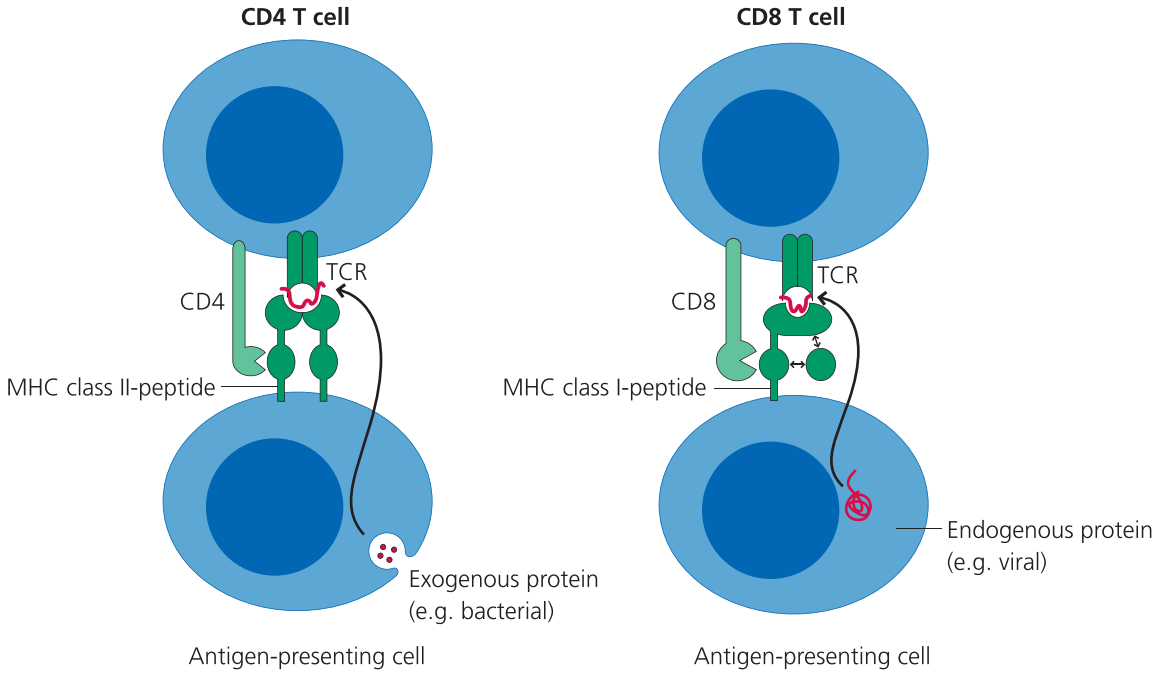

Fig. 1.28 Antigen recognition by CD4 and CD8 T cells. Conventional αβ T cells express either CD4 or CD8. **CD4 T cells** recognize peptide–MHC class II complexes. Their CD4 molecules bind to conserved regions of MHC class II molecules, helping their TCRs to recognize peptide–MHC class II complexes. The peptides bound to MHC class II molecules are derived from "exogenous" antigens from the extracellular milieu (e.g. microbial components that have been endocytosed). Only a few specialized cell types express MHC class II molecules constitutively. Activated CD4 T cells are often known as helper T cells. **CD8 T cells** recognize peptide–MHC class I molecules. The CD8 molecules bind to conserved regions of MHC class I molecules and perform an analogous function to CD4 molecules (Section 1.5.3.4) in permitting T cell recognition. However peptides bound to MHC class I molecules are typically derived from "endogenous" antigens from the intracellular milieu (e.g. components of infecting viruses in the cytoplasm). Almost all cell types express MHC class I molecules. Fully activated CD8 T cells are generally known as cytotoxic T lymphocytes (CTLs).

MHC molecules that are present in any individual. Third, MHC genes are very polymorphic, meaning that sometimes 100 or more alleles of a given MHC molecule exist within the population (e.g. humans). This means that the chances of any given individual sharing exactly the same set of MHC molecules as another is extremely small, except in the case of identical twins. Inevitably, because of the particular set of MHC molecules they possess, some individuals may be able to respond better to some infectious agents than others. Hence, the extensive diversity of MHC molecules within a population is extremely important to ensure survival of the species as a whole – even if some individuals are killed by any given infectious agents, it is likely that others can survive and reproduce.

1.5.4 Cytokines and Cytokine Receptors

Cytokines are small, hormone-like proteins produced by many different cell types, including the cells of immunity. They work by binding to cytokine receptors which are expressed by many different cell types, again including the cells of immunity. In the immune system, cytokines help to bring about an integrated and coordinated response appropriate to the type of infection that has occurred. Cytokines can act locally on the same or different cells, in an autocrine or paracrine manner; some also can act on more distant cells or tissues in an endocrine manner. Cytokine receptors, as well as cytokines themselves, can be grouped into different structural families; for example, some cytokine receptors comprise multiple subunits, one of which can be shared between all in the family. Some pairs or groups of cytokines tend to be involved in "cross-talk" between particular cell types of immunity, such that a cytokine produced by one cell may trigger a second cytokine to be produced by another cell that then feeds-back to enhance or inhibit the functions of the first.

Any given cytokine may have multiple functions, depending on which cell types express the corresponding cytokine receptor. The overall effects of cytokines are mediated by the different responses that the respective cell types make. Cytokines are involved in both innate and adaptive immunity, often both. Below, to provide some examples we will briefly consider these responses separately, but stress that this is a highly artificial and over-simplified distinction. We should also stress that some cytokines which play crucial roles in immunity are also produced by "non-immune" cells. See Figure 1.29.

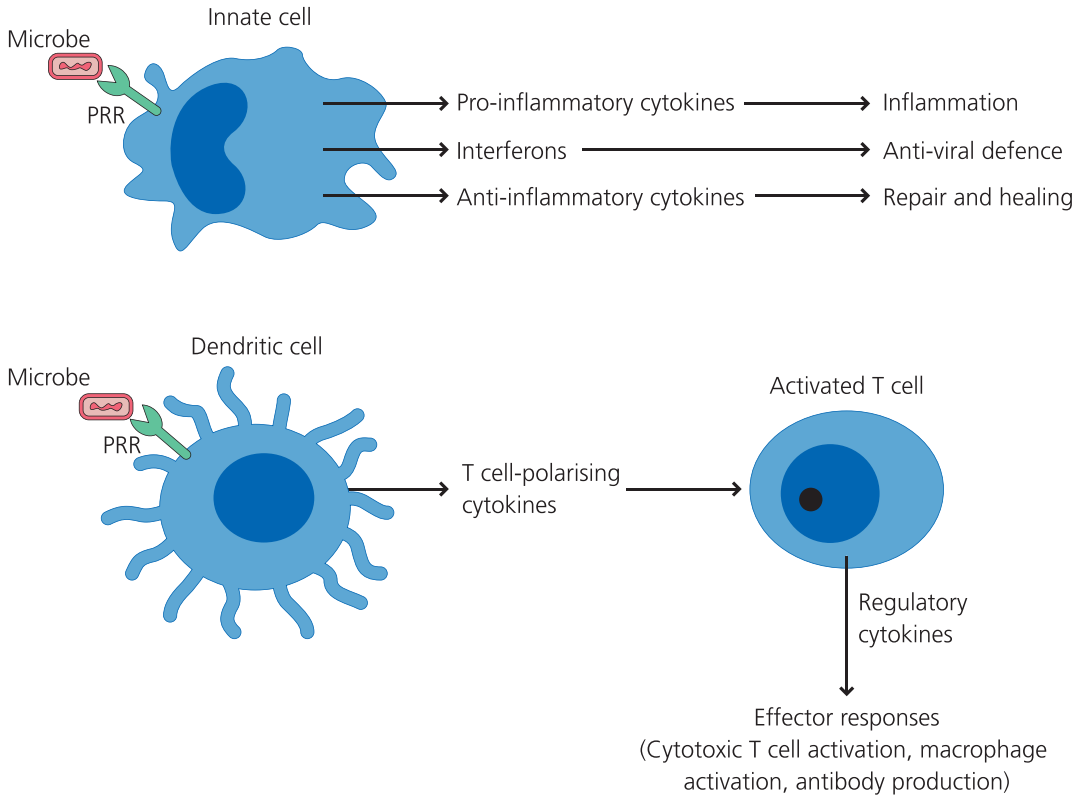

Fig. 1.29 Examples of cytokine functions. All immune (and many other) cell types can produce cytokines, which represent the main method of communication between cells that are not in direct contact with each other. Cytokines are proteins that act on other cells to alter their properties and functions. They can act on the cell that produces them (**autocrine**), on local cells (**paracrine**) or distantly (systemically – **endocrine**). They can be involved in activation or inhibition of cell functions. Some general functions of cytokines that play particularly important roles in innate and adaptive immunity or which help link these two arms are indicated. These are, however, gross over-simplifications. Not shown is another class of specialized cytokines, chemokines, that play important roles in regulating cell migration and localization, and which can be produced by all cell types indicated.

1.5.4.1 Cytokines in Innate Immunity

Cytokines are produced by all innate cells including macrophages, granulocytes, mast cells and NK cells. Some cytokines are particularly efficient at stimulating inflammatory responses and are therefore termed pro-inflammatory cytokines. For example, some cytokines induce local endothelial cell responses, leading to increased permeability and leukocyte recruitment. Some also act on distant tissues, including bone marrow, liver and hypothalamus, and contribute to systemic inflammatory responses. Other cytokines are particularly efficient at inhibiting inflammatory responses; these are termed anti-inflammatory cytokines. Some may also help to stimulate wound repair, healing and tissue remodelling, including the stimulation (or inhibition) of growth of new blood vessels (angiogenic effects). Some of these cytokines, and others produced by DCs, also play very important roles by acting on the cells of adaptive immunity and polarizing their responses (e.g. to induce different types of CD4 T cell responses).

A specialized group of cytokines is the interferons (IFNs), all of which have anti-viral activity. Type I IFNs are very powerful anti-viral agents; these include the α- and β-IFNs. They are secreted by virally-infected cells and some activated leukocytes, such as macrophages and pDCs. They act on other cells to induce an anti-viral state by inducing molecules involved in inhibition of viral protein synthesis. Type I IFNs also regulate other immune cells. Type II (γ) IFN is a relatively weak anti-viral agent; however, more importantly, it is a highly potent macrophage activator that induces strong microbial killing activity in the cells. It is secreted by NK cells and activated T cells.

1.5.4.2 Cytokines in Adaptive Immunity

Many cytokines are produced by activated lymphocytes. Some of the best understood, functionally, are probably those that are produced by CD4 T cell subsets (though CD8 T cells and even B cells also secrete cytokines). Different sets of cytokines are produced by different polarized subsets of CD4 T cells. For instance, a signature cytokine secreted by T_h1 T cells is IFN-γ and, by T_h2 cells, IL-4. Together, these sets of cytokines help to orchestrate different types of adaptive immune responses. For example, different sets of cytokines are involved in stimulating B cells (once activated) to secrete different types of antibodies that can interact selectively with phagocytes and NK cells or with mast cells and eosinophils.

Generally speaking, cytokines can be thought of as soluble molecules that bind to their respective cellular receptors. However, certain cell surface molecules that are involved in communication between cells may also be structurally related to certain cytokines and their receptors, and are thus said to belong to a cytokine–cytokine receptor family. A case in point is the TNF–TNF receptor family. Many molecules in this family play crucial roles in life or death decisions of cells. For example, the prototypic member of this family, TNF-α, can function as a pro-inflammatory cytokine in some cases, but trigger apoptotic cell death in others. Fas and Fas ligand, introduced earlier as molecules that can be used by cytotoxic cells to kill other cells, are also, structurally, members of this family.

1.5.4.3 Chemokines and Chemokine Receptors

As discussed earlier, a specialized subset of cytokines is involved in the localization and directional migration (chemotaxis) of immune cells into and within different anatomical compartments (e.g. at sites of inflammation or within secondary lymphoid tissue). These chemoattractant cytokines are hence termed chemokines. Some chemokines also have additional functions (e.g. they may have direct anti-microbial activities). Chemokines bind to chemokine receptors that are widely expressed on different types of cell. Often, several different chemokines can bind any given chemokine receptor and any given chemokine receptor can bind different sets of chemokines – the number of possible permutations and combinations is immense.

As for cytokines in general, different chemokines are produced by the different cells of innate and adaptive immunity, and help to orchestrate immune responses. For example, chemokines produced by polarized subsets of T cells can recruit more of the same subset of T cells into sites of infection, as well as other cells with which they need to interact (e.g. monocytes or granulocytes).

1.5.5 Effector Molecules of Immunity

In previous sections we have already mentioned several types of effector molecules that help to bring about the elimination of infectious agents. For example, these include perforin and granzymes that are used by cytotoxic cells to kill infected cells (Section 1.4.4). Other molecules such as defensins have direct anti-microbial functions in that they are directly toxic to microbes (Chapter 4); arguably these might also includes some of the ROIs and other toxic molecules that can be produced by phagocytes. In this section however, we will focus on two other sets of very important effector molecules in immunity: complement and antibodies. Complement is a multi-molecular system of proteins in blood and tissue fluids; it is primarily a component of innate immunity. Antibodies, secreted by B cells when they develop into plasma cells, are primarily components of adaptive immunity. However, both complement and antibodies are involved in each type of immunity (below).

1.5.5.1 Shared Functions of Complement and Antibodies

Complement and antibodies each have specialized features and functions, but some are shared between them. These include:

- **Recruitment to sites of infection.** Both are types of soluble molecules that circulate in the blood, but which can be recruited to sites of infection because local inflammatory responses increase the permeability of the endothelium, allowing them to cross into extravascular tissue spaces.
- **Formation of immune complexes.** Both can bind to soluble antigens to form complexes that may induce inflammation.
- **Opsonization.** This is the process of coating microbes, to enhance their uptake and subsequent elimination by phagocytes. Microbes coated with complement or antibodies are directed to specialized receptors, called opsonic receptors. These are respectively the complement receptors and the Fc receptors (FcRs); there are several types of each.
- **Enhancing adaptive immunity.** Components of complement and antibodies, when bound to antigens, can enhance different types of adaptive immune responses.

1.5.5.2 Complement and Complement Receptors

The complement system is a cascade in which activation of one component can lead to activation of the next – and because one activated molecule can activate several or many others, there is built-in amplification in the system. The complement system can be activated by three different pathways. One, the mannose-binding lectin (MBL) pathway, is initiated by a soluble PRR, MBL, binding to the surface of microbes. The second, the alternative pathway, is triggered spontaneously and serves to amplify the other two pathways. The third is the classical pathway, activated by complement binding to antibodies on the surface of microbes. In addition to their roles in opsonization of microbes and enhancing B cell responses (above), binding of complement to some microbes can lead to the assembly of other components that form a pore in the membrane, leading to direct lysis of the microbe. Other complement components diffuse away from the site of activation and are involved in stimulation of inflammation (e.g. by binding to different types of complement receptors on endothelial cells or mast cells). Complement also plays an important role in helping to solubilize and clear immune complexes from the blood. As with all cascade systems, the complement pathway is tightly regulated to help limit damage to host cells; in many cases this regulation is mediated by enzymes that cleave and inactivate active components. See Figure 1.30.

1.5.5.3 Antibodies and Fc Receptors

Different types or classes of antibodies are classified according to the type of constant region that they contain. In humans and mice these are called IgM, IgG, IgA, IgE and IgD (there are other types in species such as fish). All can be secreted as soluble antibodies although IgD exists mainly as a cell-bound form. In addition to these main classes of

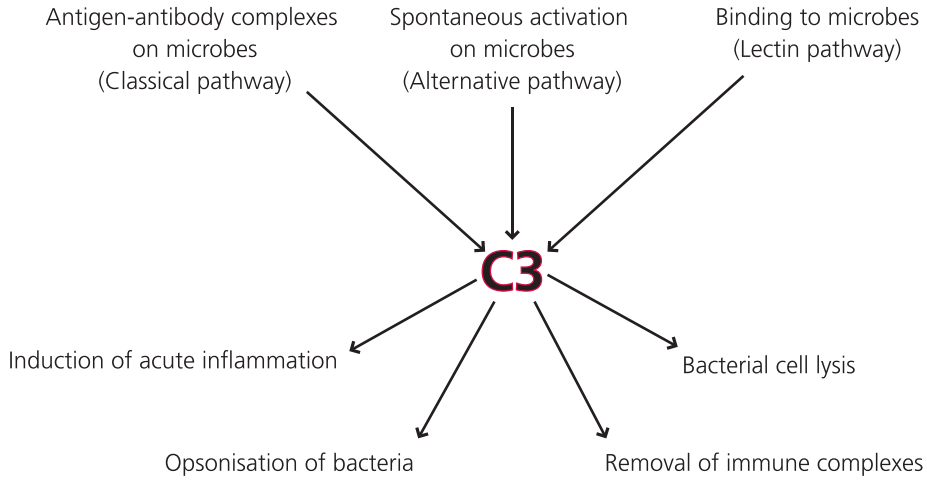

Fig. 1.30 Activation and functions of complement. The complement system comprises many different proteins, some of which form a proteolytic cascade that becomes activated during innate and adaptive responses. Complement can be activated by three different routes. Typically the lectin pathway is triggered directly by some microbial structures, the classical pathway is triggered by some types of antibodies, and the alternative pathway acts as an amplification loop for the former two. **Convergence at C3**. Activation of complement by any of these pathways leads to activation of the central C3 component, after which the pathways are identical. **Functions of complement**. Complement activation has four main outcomes. (i) Binding of complement components to the surface of microbes can opsonize them, promoting phagocytosis via complement receptors. (ii) Small complement fragments help to trigger local inflammatory responses. (iii). Activation can help to solubilize or eliminate large antibody–antigen immune complexes. (iv). The late complement components can assemble into pores in microbial membranes and (in some cases) kill them.

antibody, there are also subclasses of some of them, such as the different forms of IgG that have different functions. The different functions of different types of antibody are determined exclusively by their constant regions.

Different classes of antibodies are generally found in different compartments of the body. For example, IgM and IgG are commonly found in blood and at sites of inflammation, and IgG can also cross the placenta to the foetus. In contrast, IgA is typically secreted into mucosal sites (e.g. the gut) and into maternal milk of mammals from where it can be delivered to neonates. IgE is present at low levels in blood, but binds with high affinity to mast cells in tissues.

Different classes of antibody also have very different functions. As noted (above) some antibodies can help to opsonize microbes, directly or indirectly by activating complement. IgM, which generally has a pentameric structure (five "Y"-shaped monomers linked together) cannot act as an opsonin on its own, but is particularly efficient at activating complement. Some types of IgG are very good opsonins and in some cases they also enhance the killing of the microbes by phagocytes. IgA, which in mucosal tissues is largely dimeric, and some types of IgG are very efficient at "neutralization" – the capacity to bind to a virus, bacterium or bacterial toxin and prevent it from infecting or acting on cells. IgE is a very good "sensitizer" of mast cells – when antigen binds to IgE that is attached to mast cells or eosinophils, it stimulates degranulation and the mediators that are released help to stimulate inflammation and may be toxic to microbes or larger parasites. See Figure 1.31.

1.5.6 Cell Signalling Components

In general, receptor molecules associated with cells are linked to intracellular components that can transduce signals. Signal transduction is initiated when a receptor recognizes its ligand. This stimulates different intracellular biochemical cascades (signalling pathways). Some of these signals ultimately act on the cytoskeleton so the cell can change shape, internalize molecules or particles, or move. Others increase or decrease the susceptibility of a cell to apoptosis, thus regulating cell survival. Still others can signal to the nucleus, activate transcription factors and alter gene expression, and hence the proteins that are synthesized within that cell.

Any given receptor may be expressed on more than one cell type and similar receptors may often deliver signals in similar ways. However, the outcome can be very different depending on the type of cell that is involved. Part of the difficulty in understanding signal transduction is that the names of components are very complex. However, some of the principles are fairly straightforward. Many signal transduction pathways involve enzymes such as tyrosine kinases which introduce phosphate groups onto intracellular tyrosines in other proteins, and tyrosine phosphatases which counter the effect of the kinases by removing phosphate groups. Phosphorylated tyrosine residues can be recognized by the so-called SH2 domains of other signalling components. An example is the JAK–STAT pathway that is used by many cytokine receptors (above) JAKs (Janus kinases) are tyrosine kinases and STATs

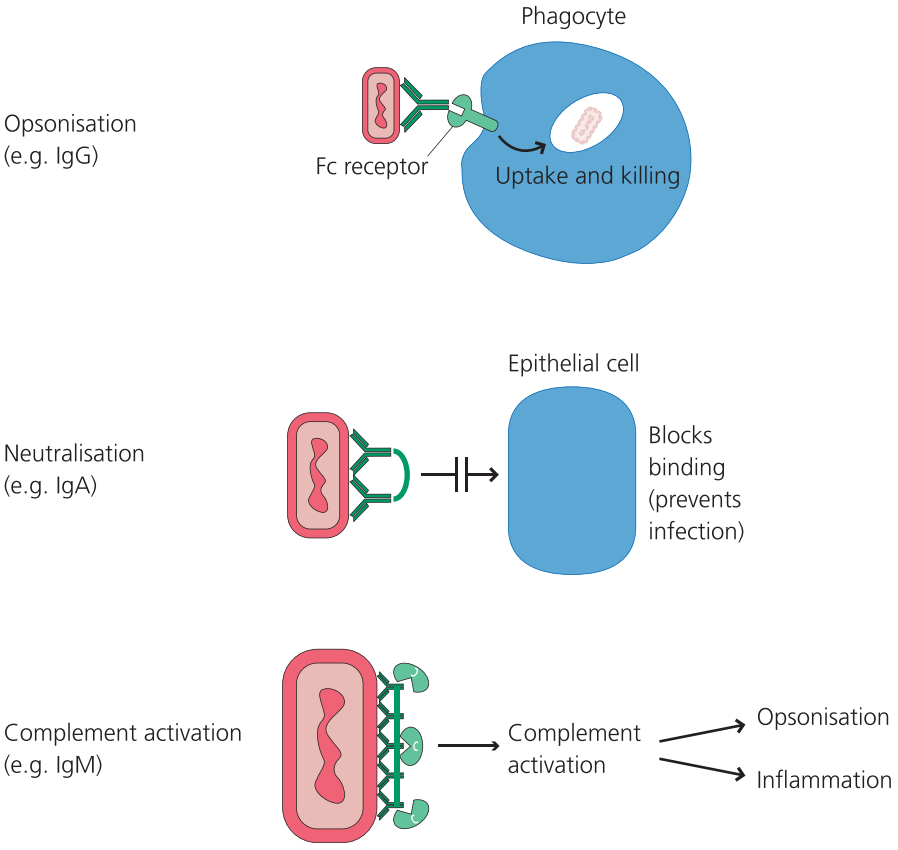

Fig. 1.31 Some functions of antibodies. Antibodies are of different classes: IgD, IgM, IgG, IgA and IgE. These all comprise the typical immunoglobulin monomer (a "Y"-shaped molecule), but in some cases they can form multimers, particularly IgA and IgM. Some classes, such as some types of IgG, are important opsonins, binding to microbes and targetting them to phagocytes through specific FcRs. Several classes, such as IgA in the gut, can bind to microbes and inhibit their attachment to host cells; by thus preventing infection they neutralize the microbe. Particular classes, including IgM, are very efficient at activating complement, thus indirectly leading to opsonization or inflammatory responses (mediated by activated complement components).

(signal transducers and activators of transcription) contain a SH2 domain that allows them to bind to the JAKs. In turn, the STATs are phosphorylated, dimerize and translocate to the nucleus where they act as transcription factors to regulate gene expression. Some signal transduction modules also use G-proteins that act as molecular switches. Examples of G-protein-coupled receptors (GPCRs) are the chemokine receptors (above). Signalling pathways may also contain adaptors that help one component bind to another and scaffolds on which several components can be attached to facilitate their coordinated functioning, particularly in specific intracellular locations. See Figure 1.32.

1.6 Immune Responses and Disease

As will become evident in other chapters, the absolute necessity for an immune system is shown by the life-threatening infections that can occur when it is defective. In addition, the immune system has enormous power to attack the body itself or to make damaging, sometimes fatal, responses to otherwise harmless agents. The immune system is also very complex. This is evident from the problems we have in understanding and preventing the rejection of transplants or the development of cancer. The immune system has, however, huge potential, only partially realized as yet, in the development of strategies for the treatment of disease.

In this last section we first outline some problems of immunity in terms of one particular problem the immune system has faced during its evolution and the different problems that result from defective, aberrant or unwanted immune responses. Finally, we introduce two therapeutic approaches designed to manipulate immunity for our own benefit.

1.6.1 The Adaptive Immune System Needs to be Educated

1.6.1.1 The Problem of Self–Non-Self Discrimination

The immune system has evolved to have a defensive role against any infectious microbe, but should not cause harm to the body. In order to do this, the immune system must be able to discriminate between harmless components of the body (self) and components such as food and commensal bacteria, which should not be attacked, and those foreign agents such as potential pathogens, which do need to be attacked. Although this is often called self–non-self discrimination, more accurately it could be called harmful–harmless discrimination. The normal non-reactivity of the immune system towards harmless antigens is called tolerance.

1.6.1.2 Immunological Tolerance

How does the immune system discriminate between harmful and harmless? We have briefly touched on this earlier (Section 1.2.3.3). The evolution of innate immunity has led to the development of PRRs, some of which recognize components of infectious agents that are not synthesized by

the host. In this sense, PRRs, by their very nature, may provide perfect discrimination between harmless self and harmful infectious non-self. Thus, non-reactivity in innate immunity is essentially passive. However, there is a big problem in terms of adaptive immunity. The specificity of all lymphocyte antigen receptors, the TCRs and BCRs of lymphocytes, is largely generated at random (Section 1.5.3.2). This means that many of these receptors will potentially recognize self and there is very good evidence that this does occur, as we shall see later (Section 1.6.4). Such receptors are termed autoreactive receptors. They include autoantibodies that can cause much damage and lead to autoimmune diseases. Hence, there have to be active mechanisms of tolerance to prevent lymphocytes bearing these receptors from being produced in the first place and/or to inhibit the responses of any lymphocytes that might develop with such receptors. Both mechanisms occur, but at different times and in different places.

The first mechanism for inducing tolerance occurs during the early development of B cells in the bone marrow and of T cells in the thymus. If a developing B cell or T cell expresses an antigen receptor that can bind to any self component with sufficient strength (affinity), that cell can be either killed or inactivated; these two outcomes are termed clonal deletion and anergy, respectively. In the case of B cells, unlike T cells, they have the further option of changing their antigen receptors if they recognize self antigens; this is termed receptor editing. Since these processes occur in central or primary lymphoid tissues (as opposed to peripheral sites or secondary lymphoid tissues) these forms of tolerance are known as central tolerance. This process is, however, imperfect. For example, it is impossible to ensure that every single one of the self components that is produced throughout life is represented in the tissues where lymphocytes develop; think, for example, of the new hormones and proteins that are produced during puberty or during pregnancy and lactation. Hence, despite the efficiency of central tolerance, some mature autoreactive T cells and B cells are inevitably released from bone marrow and thymus. See Figure 1.33.

The second mechanism of tolerance induction occurs in the periphery (peripheral tolerance). It differs somewhat for T cells and B cells. In the case of naïve T cells, normal activation

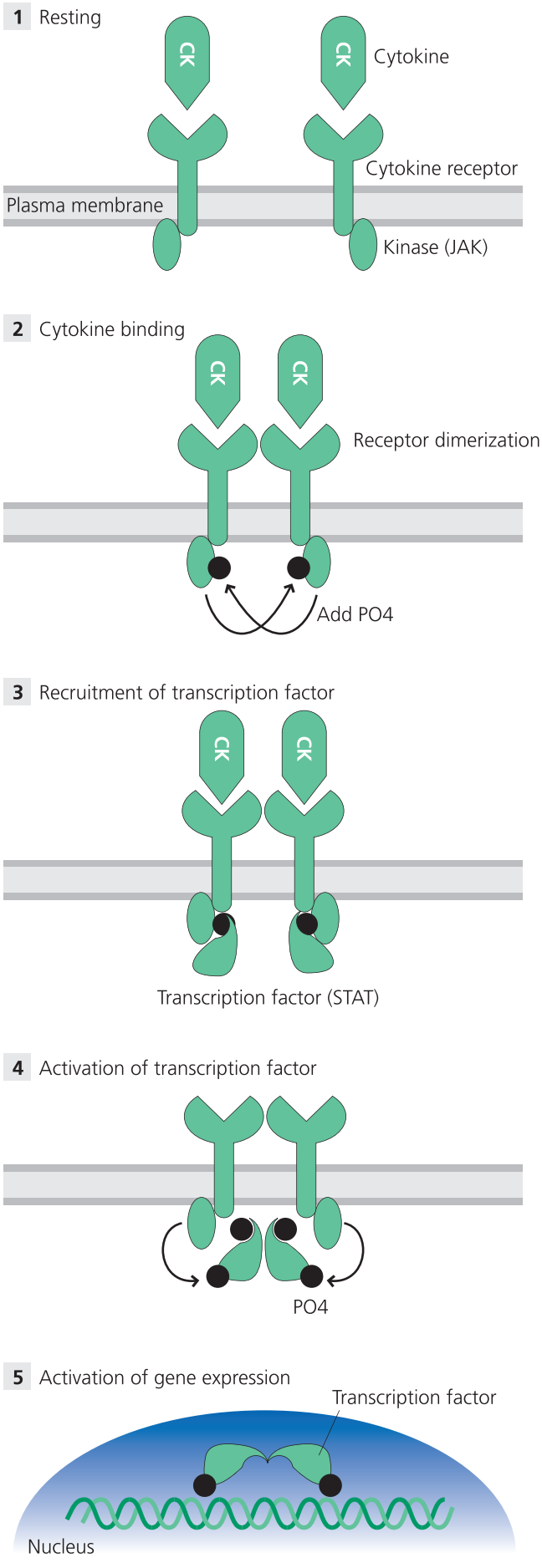

Fig. 1.32 An example of an intracellular signalling pathway. A number of cytokine receptors signal through the JAK–STAT pathway. These receptors are associated with tyrosine kinases called JAKs. Binding of a cytokine leads to dimerization of the receptors and juxtaposition of the JAKs which phosphorylate and activate each other. This enables STATs to bind (they have SH2 domains which recognize phosphorylated tyrosines). The JAKs phosphorylate the STATs, which then translocate as a dimer to the nucleus, bind DNA and act as transcription factors to change gene expression. This is a very simple signalling pathway that does not involve other molecules as adaptors or scaffolds to help link or localize different components of the pathway.

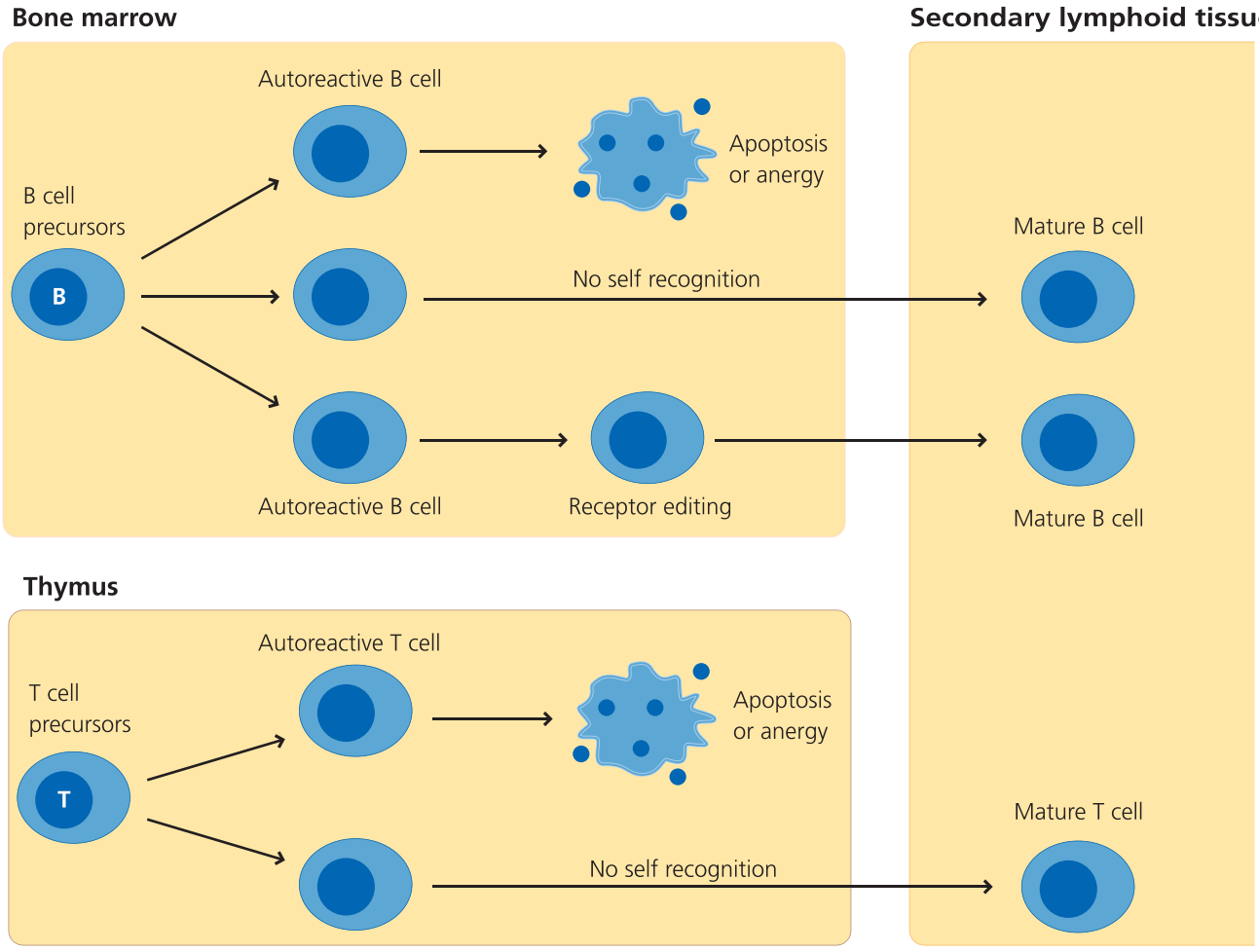

Fig. 1.33 Some mechanisms of tolerance induction. As B cells and T cells generate their respective antigen receptors largely at random (Figure 1.23) many have a high risk of recognizing components of the host itself (e.g. structural components of tissues or other cells of the body) – such receptors are termed autoreactive. Generally speaking, during lymphocyte development, cells with autoreactive receptors are killed through the induction of apoptosis (clonal deletion) or rendered unresponsive (anergy). Both apply to B cells developing in the bone marrow; the former particularly applies to T cells developing in the thymus. In addition, B cells can try to make another receptor that is not autoreactive (receptor editing). The remaining cells mature, expressing receptors are generally not able to recognize self components – hence they are tolerant – but they can potentially recognize foreign antigens should they be encountered in the future.

needs two sets of signals, including specialized costimulatory molecules that are generally expressed by DCs but not by most other cell types. Hence, if a T cell recognizes a self antigen on most other cell types that do not express costimulatory molecules, activation cannot occur; instead the cell becomes unresponsive or dies. In addition, regulatory T cells, of different types, can develop to suppress immune responses. In the case of B cells, many responses need T cell help (e.g. in the production of antibodies against protein antigens). In the absence of such help, a B cell that has recognized antigen does not become activated or in other cases is anergized and subsequently dies. This implies that T cell tolerance needs to be more complete than B cell tolerance and this is what is actually observed.

1.6.2 Immune Responses Against Infection Can Cause Damage

1.6.2.1 Immunity is Generally Beneficial

Having an immune system is of course essential for defence against infection. The rapid activation of innate and adaptive immunity often means that even if we become infected the infectious agent can be cleared without us even being aware of this happening; this is termed a subclinical infection.

1.6.2.2 Normal Immunity Can Cause Problems

Sometimes, however, immune responses can lead to unpleasant symptoms (think of how you feel if you are fighting a cold or flu) and may even cause long-lasting tissue damage, as in

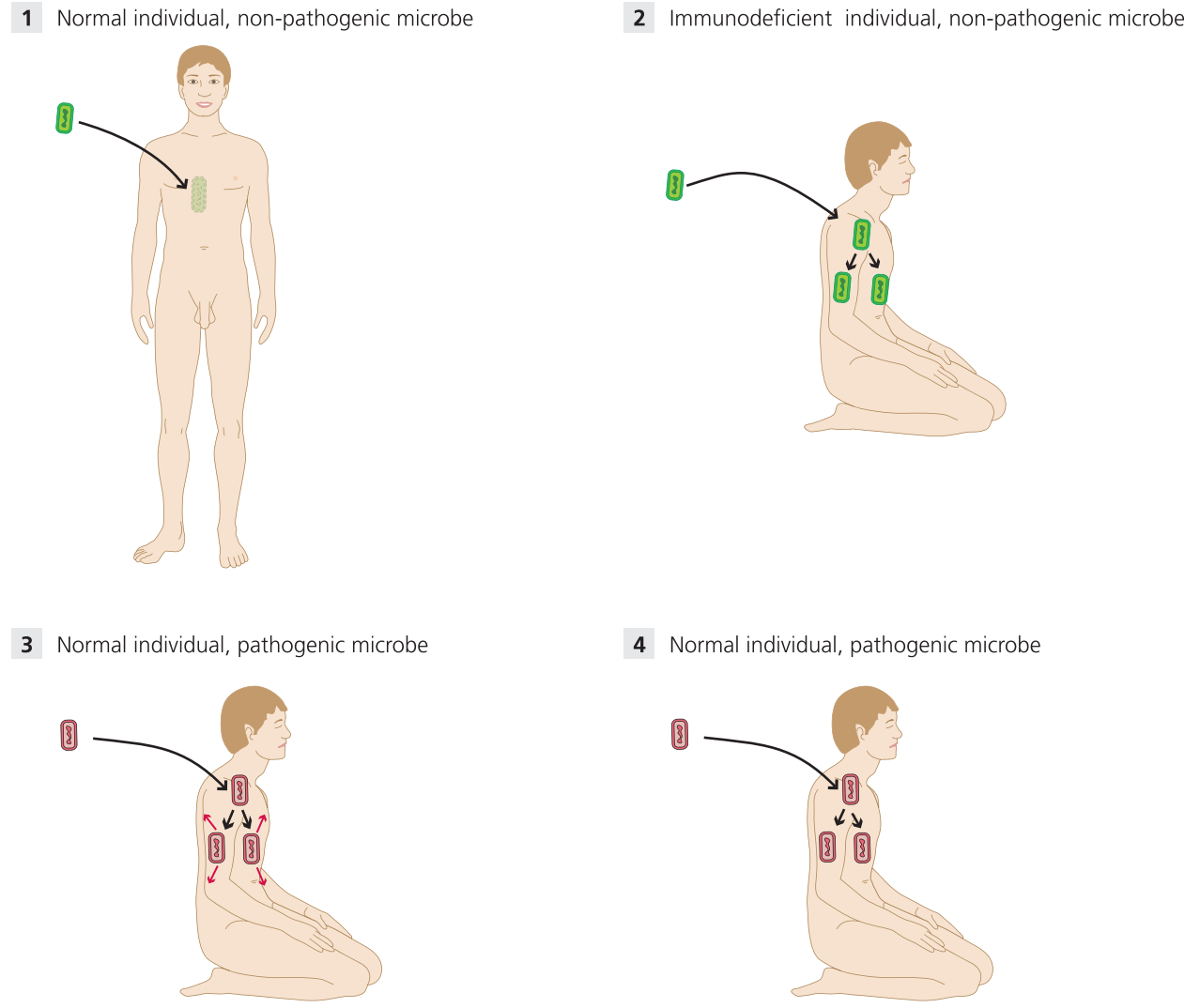

Fig. 1.34 Infection, disease and tissue damage. (1) In healthy (normal) individuals with functional immunity, many non-pathogenic microbes are eliminated without causing disease, subclinically. (2) In immunodeficient individuals these same microbes may cause disease (Section 1.6.3). (3) In normal individuals infected with some pathogenic microbes, secretion of toxic molecules or other mechanisms can cause disease. (4) In some normal individuals, the immune response to the microbe is the actual cause of clinical disease – collateral damage.

the lung of someone with tuberculosis. This is because the highly potent mechanisms that are involved in fighting infections can cause side-effects and sometimes significant collateral damage ("friendly fire"). These are examples of how normal immune responses to "infectious non-self" antigens can cause problems. See Figure 1.34.

A further problem arises because viruses and microbes can evolve so much faster than the host's immune system. The efficiency of the many components of immunity in dealing with infections means that the immune system itself helps to drive the evolution of infectious agents. In other words, it exerts considerable pressure to select infectious agents with mutations that allow them to evade immune responses. In this way an infectious agent, that would otherwise be cleared, may actually become a pathogen. Pathogens are successful because they evade, or subvert, immune responses and the diseases that they cause can sometimes be due to collateral damage caused by host immunity.

We discuss the benefits of immunity in relation to these problems and provide further examples of them, particularly in Chapter 2, and we will also meet them again from time to time in Chapters 3–6. For now we will introduce the ways in which defects in immunity lead to disease and how misdirected or unwanted immune responses can cause harm; these are discussed in more detail in Chapter 7.

1.6.3 Defects in Immunity Can Cause Serious Infections

The importance of an effective immune system is shown most clearly by the increased frequencies of infectious diseases seen in patients with defective immunity.

1.6.3.1 Primary Immunodeficiency Diseases

Any genetic defect that alters the function of a component that is normally involved in elimination of an infectious agent may lead to serious infections caused by that agent. These are called primary immunodeficiency diseases (Figure 1.34). Commonly, primary immunodeficiencies are associated with mutations in the genes that encode soluble or cell-associated components of immunity, although in other cases they may, for example, result from mutations in metabolic pathways. At least 180 different mutations that lead to primary immunodeficiencies have been identified to date; there are likely to be many more. Primary immunodeficiencies may result from defects in innate or adaptive components, or both, including the following general types.

i) Defects in phagocyte functions.
ii) Defects in complement activation, function or regulation.
iii) Defects in the generation of lymphocyte antigen receptors, leading to failure of development of T cells and/or B cells.
iv) Defects in the ability of cells to cooperate (e.g. for T cells to help B cells make antibodies).

Not surprisingly, primary immunodeficiencies can therefore lead to severe, persistent, unusual or recurrent (SPUR) infections, and the type of infection that occurs reflects the normal functioning of the component or cell that is involved. We use this as evidence for the involvement of different immune components in defence against certain types of infectious agents in Chapters 2–6.

1.6.3.2 Secondary (Acquired) Immunodeficiency Diseases

Immunodeficiencies that are not caused by a genetic defect are termed secondary (or acquired). In general these immunodeficiencies do not appear in early childhood. The individual is born with a normal immune system, but a later event causes damage leading to defective immunity. In some cases the cause(s) is unknown, but in other cases this may, for example, result from aggressive treatment for cancer or as a complication of the advanced disease itself. Secondary immunodeficiencies can also be caused by infection with pathogens. A well-known example is HIV, which, because it leads to destruction of key immune components (CD4 T cells) renders the infected individual susceptible to other types of infection that can be life-threatening as the individual progresses to acquired immunodeficiency syndrome (AIDS).

1.6.4 Immune Responses Can Sometimes be Made Against the Wrong Antigens

There are circumstances where immune responses attack the body itself, or are made against otherwise harmless agents, causing disease and sometimes leading to life-threatening conditions. These conditions are of two main types.

- Aberrant responses against self antigens, which cause autoimmune diseases.
- Aberrant responses against apparently innocuous non-self antigens that result in allergies and other immune-related sensitivities (sometimes termed hypersensitivity diseases).

All of these conditions are primarily caused by aberrant adaptive immune responses, which may, however, reflect inappropriate activation of the innate immune system. With one exception (i.e. allergies), the different types of immunological mechanism involved in autoimmune diseases and other immune-related sensitivities overlap. One convenient way of distinguishing between these two types of aberrant responses is to consider whether the antigen that is ultimately recognized is "intrinsic" (i.e. a self antigen of the host itself) or "extrinsic" (i.e. a non-infectious, non-self antigen from the environment of the host, such as pollen in those who suffer from hay fever). In most cases we do not fully understand why such responses are triggered, although often we can appreciate the underlying mechanisms that lead to disease. These conditions are considered more fully in Chapter 7. See Figure 1.35.

1.6.4.1 Autoimmune Diseases

Despite the varied mechanisms of immunological tolerance (above), immune responses are sometimes triggered against normal self components, leading to autoimmune disease. Perhaps one of the simplest mechanisms to understand is when normal mechanisms of tolerance induction are defective. This could be due to a defect in central and/or peripheral tolerance of T cells. An example of the former is if there is a failure to express self antigens, to which T cells are normally tolerized, in the thymus. An example of the latter is if regulatory T cells are not induced. Both types of defect lead to very serious autoimmune diseases and widespread tissue damage and are further discussed in Chapter 5.

Other types of autoimmune disease occur through different mechanisms, considered in Chapter 7. For most of these we understand the mechanisms causing the disease, but we do not understand why it occurs. They can be classified as follows, although more than one mechanism may be involved in any given disease:

- The activation of autoreactive B cells and the secretion of antibodies against normal self components, termed autoantibodies. These can lead to cytotoxic effects and tissue damage that is mediated by the cells with which they interact. Alternatively, they can directly inhibit the normal functioning of other cells of the body (e.g. because they block the binding of molecules to their receptors). An example of the latter is myasthenia gravis where an

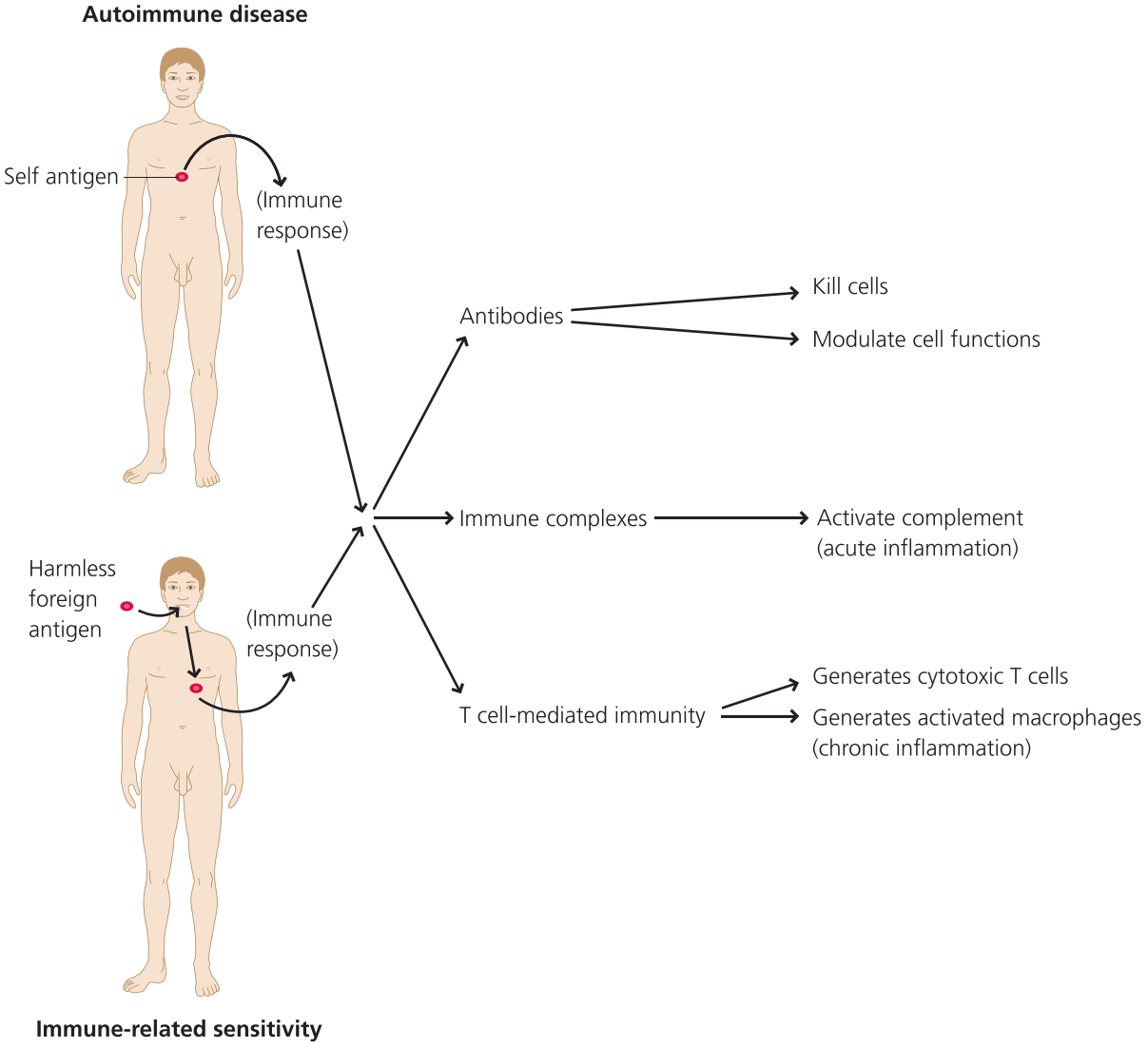

Fig. 1.35 Autoimmune diseases and immune-related sensitivities. Disease can result from activation of adaptive immune responses against otherwise harmless ("intrinsic") components of the body itself or against non-infectious ("extrinsic") foreign agents from the environment. The effector mechanisms causing the tissue damage may be mediated by antibodies of different types, large immune complexes, T cells that aberrantly activate macrophages or cytotoxic T cells, or a combination of these. Symptoms can be mild (e.g. skin rashes) to life-threatening (e.g. anaphylaxis following a wasp sting in a sensitized individual). The clinical pattern of disease usually reflects the distribution of the antigen being recognized and may be localized to particular organs or become widespread throughout the body (**systemic**).

antibody blocks the transmission of nerve impulses to muscles, leading to progressive paralysis.

- The production of immune complexes composed of antigens bound to antibodies and/or complement either in specific tissues or in the circulation. If circulating immune complexes are not effectively removed they can induce inflammation that may prevent normal functioning of certain organs. An example of the latter is the kidney damage seen in serious cases of systemic lupus erythematosus.
- The induction of T cell-mediated responses against self antigens. This is responsible for autoimmune diseases such as insulin-dependent (Type I) diabetes. Here the T cell responses involve the activation of cytotoxic T cells or activated macrophages that are, in turn, the main mediators of damage.

1.6.4.2 Immune-Related Sensitivities (Hypersensitivity Diseases)

In some cases, for reasons that are often not understood, an apparently innocuous antigen, which is not related to an infectious agent, can trigger aberrant responses that cause tissue damage. Perhaps the best well-known example of this is allergy (for which there is no known equivalent mechanism of autoimmunity). Examples are hay fever and food sensitivity. Allergy is caused when a specific type of antibody, IgE, is made against an extrinsic antigen, such as a component of pollen or

peanuts. IgE then binds to mast cells with no deleterious effect. However, if the antigen is encountered again, it binds to the IgE that is coating the mast cells and triggers explosive degranulation of the cells. The mediators produced then cause the symptoms and side-effects of allergy that can, in severe cases, include obstruction of the airways, cardiovascular shock and death.

The mechanisms underlying other types of immune-related sensitivities are shared with those of autoimmune diseases. As such they include diseases caused by antibodies, immune complexes and T cells. Examples of antibody-mediated disease include drug sensitivities, such as where IgG antibodies are made against penicillin. Immune complex-mediated diseases include a wide variety of "occupational" sensitivities such as Farmer's lung, in which inhaled fungal spores in mouldy hay cause immune complexes to form and trigger inflammation in the lungs. T cell-mediated diseases include contact sensitivities, in which T cells are involved in directing damaging inflammatory responses against small molecules such as metals in jewellery. The presence of pre-formed antibodies against extrinsic antigens generally leads to rapid responses called immediate-type hypersensitivities. In contrast, T cell-mediated responses against extrinsic antigens (as well as certain pathogens such as tuberculosis) are often called delayed-type hypersensitivity(DTH) responses as it takes a day or so after antigen administration for the response to become apparent.

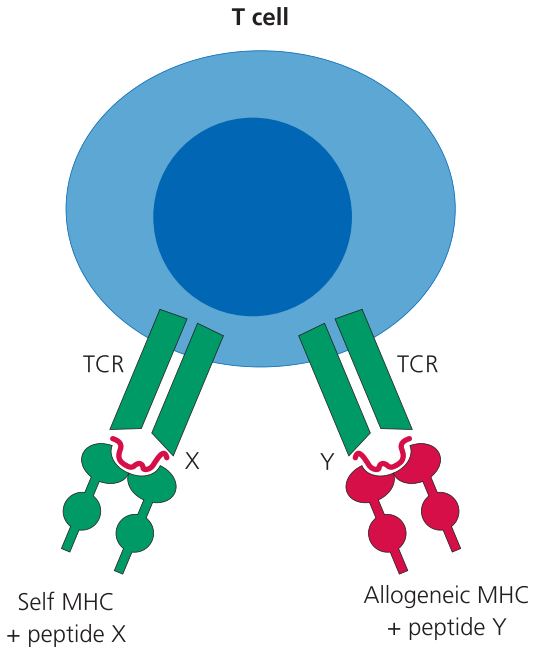

Fig. 1.36 Alloreactivity. Transplants between non-identical members of the same species (allografts) are rejected with surprising vigour because a very high frequency of T cells from any individual can recognize MHC molecules of a genetically different (allogeneic) individual. This very high frequency represents cross-reactive recognition; a T cell that can potentially recognize a foreign (e.g. microbial) peptide bound to a self peptide–MHC may also recognize an allogeneic MHC molecule(s) binding a different peptide(s).

1.6.5 Transplantation Reactions

The immune responses that occur when a foreign organ is transplanted and which often lead to rejection of the transplant are quite normal immune responses. However, in this setting they are unwanted. There are different types of rejection that occur for different immunological (and non-immunological) reasons.

1.6.5.1 Acute Rejection

Acute rejection of a transplant typically occurs within days or weeks of transplantation of a graft from a genetically different (allogeneic) individual of the same species. It is initiated by the activation of the recipient's T cells against foreign molecules present in the transplant that are termed transplantation antigens. The most important transplantation antigens are the foreign MHC molecules of the grafted tissue. T cells which would otherwise recognize peptide–MHC complexes during responses against infectious agents mount a response against the transplant because their antigen receptors (TCRs) can cross-react with foreign MHC molecules (and their bound peptides). This form of recognition is termed alloreactivity. It turns out that there is a relatively large number of alloreactive T cells in any individual, so a very substantial T cell response can be made against the foreign organ. As CD4 T cells control the responses of other cell types, allograft rejection usually involves the activation of different components of both innate and adaptive immunity. See Figure 1.36.

1.6.5.2 Other Types of Rejection

Other types of rejection are the much faster phenomenon of hyperacute rejection, when a transplant is rejected within a few minutes or hours, and the much slower phenomenon of chronic rejection that can occur even years after transplantation. The bases of these types of rejection are covered in Chapter 7. However, we will note for now that hyperacute rejection is triggered by the presence of pre-formed antibodies against the graft (e.g. because of an immune response to a previous transplant). A similar mechanism can often lead to rapid rejection of transplants between species (xenografts), such as if a pig kidney is transplanted to a human. We still do not know exactly why chronic rejection occurs.

1.6.5.3 Graft Versus Host Disease

The ability to replace defective or damaged cells or tissues by transplanting stem cells from normal individuals holds huge therapeutic potential. Bone marrow transplantation is by far the most successful example of this approach in current use. As stem cells in bone marrow can replace any and all

haematopoietic cell types, this procedure is widely used for the treatment of many primary immunodeficiencies in which a defective component needs to be replaced (Section 1.6.3.1). It is also commonly used after treatment for leukaemia, because the drugs that are used to kill the leukaemic cells also kill the normal stem cells, so these can be replaced from a bone marrow transplant. One problem with bone marrow transplantation, however, is graft versus host disease (GVHD). Recipients who receive a bone marrow transplant are either incapable of rejecting the transplanted cells because of their underlying immunodeficiency or they have been immunosuppressed to prevent rejection of the transplant. The bone marrow, however, contains mature T cells from the donor. These cannot be rejected but can recognize the recipient's MHC antigens because of alloreactivity (Section 1.6.5.1). Hence, these donor T cells can become activated and generate an immune response against host tissues, often including the skin and gut. This is GVHD – the opposite of the host versus graft responses that occur during different types of graft rejection (above).

1.6.6 Tumours Can Evade the Immune System

Tumours are caused by the uncontrolled growth of cells. Benign tumours remain localized, but malignant tumours (cancers) can spread to other parts of the body (metastasis) – this is why they can be lethal. Tumours of course originate from self cells. This is seriously problematic because of the powerful mechanisms of tolerance which generally ensure that immune responses are not made against self. In many cases, however, tumours can express antigens that can potentially be recognized by the immune system. These include viral antigens if an oncogenic virus has provoked the abnormal growth of cells, as well as components of the host that have become mutated, over-expressed or abnormally expressed (e.g. those that are normally expressed only in the foetus). Hence, some tumours can potentially be recognized by the immune system. The antigens of tumours that can be recognized by T cells and antibodies are called tumour antigens.

A further problem arises because tumours are very good at evading immunity. Thus tumours can down-regulate molecules that are needed for immune recognition, such as the MHC molecules that are normally needed for T cell recognition. In addition, tumours can secrete molecules that have powerful inhibitory effects on cells of the immune system such as DCs or they can trigger the production of cells that suppress immune responses such as regulatory T cells. We have mentioned previously that the immune system itself can select variants of microbes that are resistant to defence mechanisms and exactly the same can happen with tumours. Malignant tumours have a very high mutation rate and any tumour cell that mutates in a way that enables it to resist defence mechanisms will have a selective advantage over the rest of the tumour. This is an example of Darwinian selection occurring within a single organism. See Figure 1.37.

1.6.7 Immune-Based Therapies

We conclude this section by briefly introducing two therapeutic approaches that are allowing us to modulate immunity for our own benefit. These are vaccines, which are hugely successful in preventing some disease, but which are ineffective or do not exist for others, and therapeutic antibodies which are showing real benefit in the treatment of disease. The development of vaccines originated from empirical observations made in the days before anything was known about the immune system itself, while the development of therapeutic antibodies has only been made possible from our increasingly sophisticated understanding of immunity.

1.6.7.1 Vaccines

Protection against infection can be either active, involving direct activation of the host immune system, or passive, where antibodies or immune cells are transferred to the host. One of the most effective ways of generating active resistance to infection is to have recovered from an actual infection. To infect an uninfected person deliberately in an attempt to trigger immunity is, however, risky but has been done: infection of children with virulent smallpox (variolation) was widely practiced until Jenner developed vaccination with what we now know to be the closely-related cowpox virus. Alternatively, resistance can be acquired passively. Thus, the human foetus acquires maternal IgG by transfer across the placenta and the neonate obtains maternal IgA in the early milk (colostrum). Antibodies (e.g. generated in horses) can also be given by injection to protect against potential infection, as in wounded individuals who have not been vaccinated against tetanus. See Figure 1.38.

Vaccination is an active process that is designed to mimic, as closely as possible, the infectious agent against that one wishes to induce protection and to elicit the most effective form of immunity against that agent. The enormous potential of manipulating the immune system for the treatment of disease in this way is evident from the remarkable success that vaccination has had, for example, in the global eradication of smallpox. To date, most vaccines have been designed to trigger immunity to infectious diseases in individuals before they have been infected (prophylactic vaccination). However more recently there have been increasing attempts to design vaccines for treatment of individuals with disease (therapeutic vaccination). It is crucial to understand that an effective vaccine needs two things:

- An antigen(s), against which a response is to be generated.
- An adjuvant that triggers an effective immune response.

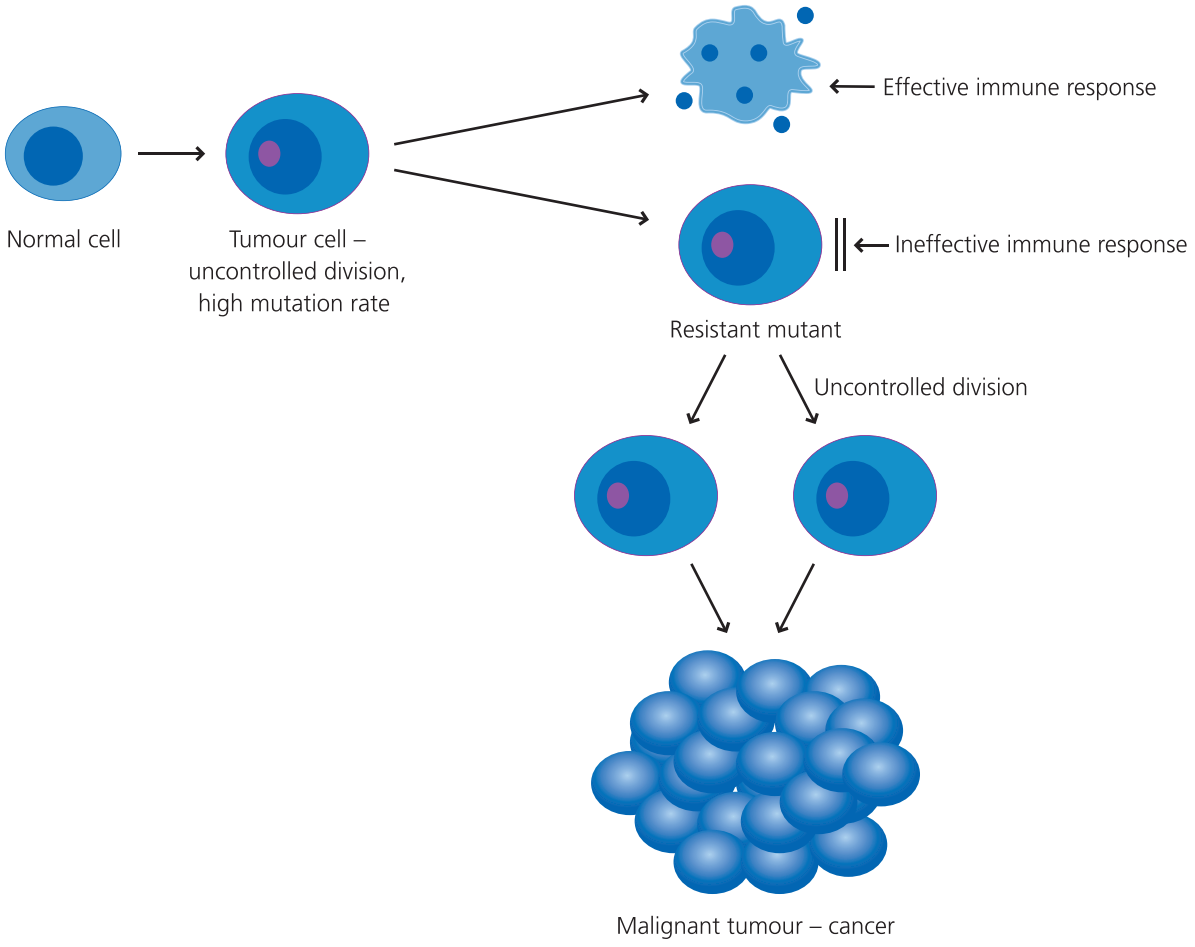

Fig. 1.37 Immune evasion by tumours. Malignant tumours (cancers) are clones of cells that have very high mutation rates. This means that many of them will express mutant proteins that can give rise to peptides not present in normal cells, which may be potentially antigenic. These peptides may induce an adaptive response to the tumour. The high mutation rate also means that new tumour variants are continually forming and, inevitably, some of these will be able to evade or avoid the immune response. (They may, for example, lose a tumour antigen, decrease MHC expression, secrete anti-inflammatory cytokines or induce regulatory instead of effector T cells). These mutant subclones will have a selective advantage and will outgrow the parental clone. Thus, over time the tumour will develop multiple means of avoiding the immune response and a cancer may develop. This is a good example of Darwinian selection in action within an individual organism.

In most cases of prophylactic vaccination against infectious diseases, protection is achieved by giving vaccines that generate active immunity. These can be live, attenuated organisms, dead organisms or parts (subunits) of organisms. These vaccines, which contain the requisite antigens and which often have intrinsic adjuvant activity, are discussed further in Chapter 2. Some vaccines are also being developed to protect against tumours. Thus, girls are now being vaccinated against the human papilloma virus (HPV) that causes carcinoma of the uterine cervix and, by preventing viral infection, initiation of the tumour is prevented.

What of therapeutic vaccines? There are situations (e.g. malignant tumours and chronic infections such as HIV) where in theory vaccines could be given to patients suffering from the disease with a view to eradicating the infection or tumour. In general, it seems much more difficult to use immune responses to treat ongoing disease than to prevent it and although many trials of therapeutic vaccination are underway, so far there are relatively few signs of real benefit. Nevertheless, progress is being made as we describe in Chapter 5 (adoptive cell therapy).

1.6.7.2 Monoclonal and Therapeutic Antibodies

Antibodies, because of their specificity, have the potential to be potent, highly selective drugs able to modulate cells and molecules *in vivo*. Until fairly recently this potential could not be realized except in a very few cases because antibodies could not be made reproducibly or in sufficient quantities. This form of treatment was revolutionized by the development of monoclonal antibodies. To make monoclonal antibodies, usually, antibody-secreting (B) cells from an

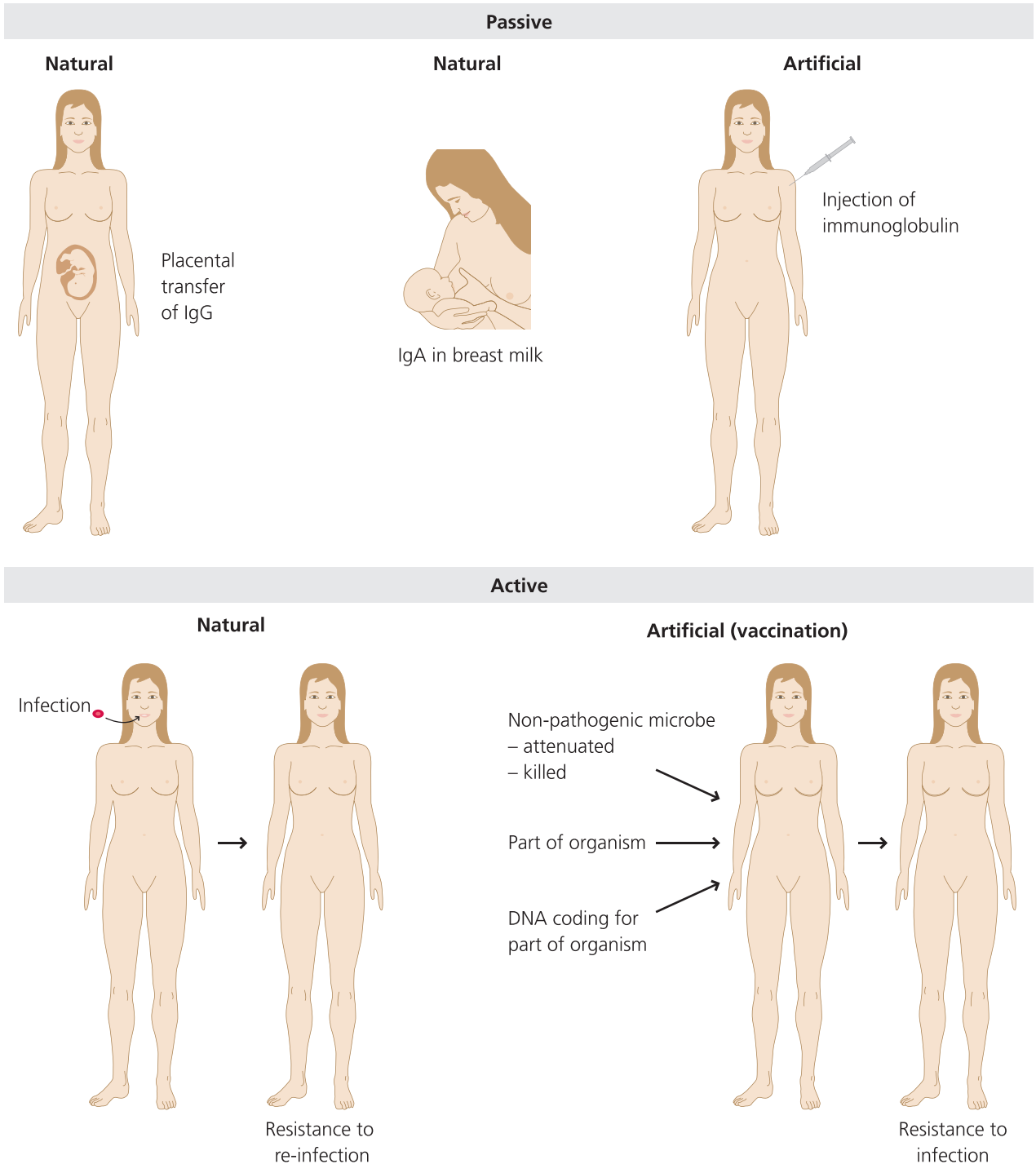

Fig. 1.38 Resistance to infection. Resistance to infection can be acquired passively or actively, through natural or artificial means. For example, passive immunity may be acquired naturally by a foetus or neonate through transfer of maternal antibodies across the placenta or in milk. It may also be delivered artificially, such as by giving pooled human immunoglobulin to antibody-deficient patients. Active immunity generally follows naturally after recovery from an infection. It may also be stimulated artificially during vaccination with a vaccine designed to induce a protective response.

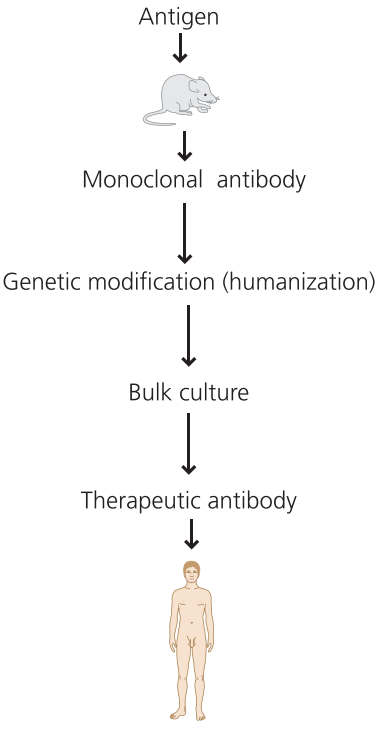

Fig. 1.39 Therapeutic antibodies. The development of monoclonal antibody technology has enabled the production of large quantities of homogenous antibodies with a defined antigenic specificity that can be used therapeutically to treat human disease. A major problem with such antibodies is that they are foreign proteins (they are typically produced in mice). The immune responses induced against them (e.g. the production of anti-antibodies) can lead to their very rapid destruction. To avoid this, genetic engineering has been used to create antibodies in which the only non-human parts are the hypervariable regions that form the antigen-binding site itself and hence are much less immunogenic. These can be used, for example, to block the activity of pro-inflammatory cytokines such as TNF-α in some autoimmune diseases, or to target molecules expressed selectively by tumour cells in certain cancers.

immunized mouse are fused with tumour cells of B lymphocytes called myeloma cells. The resulting fused cells are termed hybridomas. These are monospecific and immortal, and can be grown as clones on industrial scales. Thus, large amounts of a monoclonal antibody can be produced. Since some antibodies can inhibit or stimulate cellular responses they have huge potential as therapeutic agents. The use of monoclonal antibodies has revolutionized immunotherapy and there are now over 20 such antibodies in clinical use and many more under development. These therapeutic antibodies are being used increasingly to treat certain autoimmune diseases, to help prevent transplant rejection and to eliminate tumour cells in the treatment of some cancers. See Figure 1.39.

Learning Outcomes

By the end of this chapter you should be able to understand, briefly explain and discuss some aspects of the following topics – the relevant sections of the chapter are indicated.

- Host defence against infection (Section 1.2)
  - What are the major differences between innate and adaptive responses?
- The anatomical basis of immunity (Section 1.3)
  - What are the major differences between primary and secondary lymphoid tissues?
  - Why is inflammation important in host defence against infection?
- The cellular basis of immunity (Section 1.4)
  - What are leukocytes?
  - What are phagocytes and why are they important?
  - What are granulocytes?
  - What are lymphocytes and how many types of conventional lymphocyte are there?
  - What is immunological memory?
- The molecular basis of immunity (Section 1.5)
  - What types of molecules are involved in the migration of leukocytes from the blood into sites of infection?
  - How does recognition of infectious agents differ in innate and adaptive responses?
  - What mechanisms are involved in the generation of receptors used for antigen recognition in adaptive immunity?
  - What are cytokines and what do they do?
  - What is complement?
  - What do antibodies do?
- Immune responses and disease (Section 1.6)
  - How does the immune system normally avoid making harmful responses to self or harmless foreign molecules?
  - What is an immunodeficiency disease?
  - What different types of antigen are involved in autoimmune diseases and allergies?
  - How and why might transplants be rejected?
  - How might the immune system be able to recognize tumours?
  - How might immunity be manipulated for therapeutic purposes?