1 Basic Concepts in Immunology

1.1 The immune system

The immune system evolved so as to defend our bodies against infectious microorganisms such as viruses, bacteria, fungi and parasites. Throughout history it has been observed that people who survive an infectious disease acquire protection against that disease, which is otherwise known as immunity. As far back as the fifteenth century attempts have been made to induce immunity against infectious diseases, a process referred to as vaccination. The realisation that immunity can be transferred from one person to another demonstrated that soluble factors exist in the blood and body fluids that protect against pathogens. It is now known that cellular components of the immune system are also present throughout the entire body and that these immune cells engage with any harmful substance or microorganism in order to preserve the integrity of host tissues. The defence against microorganisms is fought on many fronts and there are immune cells and innate components of the immune system within every tissue and organ. There are a multitude of cells and soluble factors that can be considered part of the immune system. For example, the barrier function of the outer layers of the skin, the mucus produced in the airways, the antibodies secreted into the gut lumen or the circulating lymphocytes that destroy virus-infected cells. The immune system comprises a number of different cell types and a multitude of secreted factors and surface bound molecules.

The immune system has a multi-layered organisation that provides immunity to infectious organisms (Figure 1.1). Each layer of the immune system can also be considered to have an increasing complexity. The first layer is provided by physical barriers such as the skin and the mucosal epithelium of the respiratory and gastrointestinal tracts. These barriers aim to prevent pathogens gaining access to underlying tissue. The next layer is the non-specific chemical barrier that consists of antimicrobial compounds and factors of the humoral immune system (soluble factors found in body fluids). Other chemical immune defence mechanisms include the acidic environment of the stomach and the proteolytic enzymes produced in the intestines. The third layer is composed of all the cells of the immune system. Therefore, if a pathogen breaches the physical barriers and chemical barriers then the immune system utilizes its immune cells.

The cellular components of the immune system can be divided into the innate immune system and the adaptive immune system. The innate immune system provides a rapid, early response and is considered to be the first line of cellular immune defence. If the innate immune response is overcome by an infectious pathogen then the adaptive immune system comes into play. Only jawed vertebrates have evolved a complex adaptive immune system, which provides highly specific immune protection against microorganisms. The immune protection afforded by the adaptive immune system is retained by the host over a prolonged period of time and is capable of generating immunological memory. It is this immunological memory that confers immunity to subsequent infections with the same pathogen.

1.2 Tissues and cells of the immune system

The organs and tissues of the immune system can be compartmentalized (Figure 1.2). There are certain areas that are more susceptible to infection than others and these usually correspond to areas that come into contact with the environment. Therefore the mucosal immune system has evolved over millions of years in answer to selection pressures forced upon it as a result of host-pathogen interactions. The immune system therefore comprises a series of specialized organs and tissues that function by counteracting the threat of pathogens. The areas of the body at

Immunology: Mucosal and Body Surface Defences, First Edition. Andrew E. Williams.

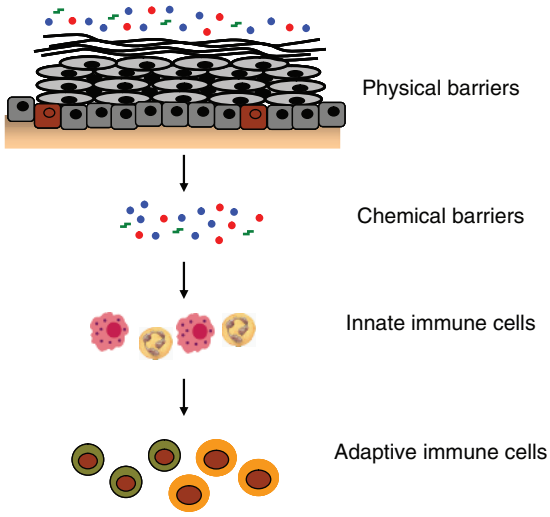

Figure 1.1 The multiple layers of the immune system.

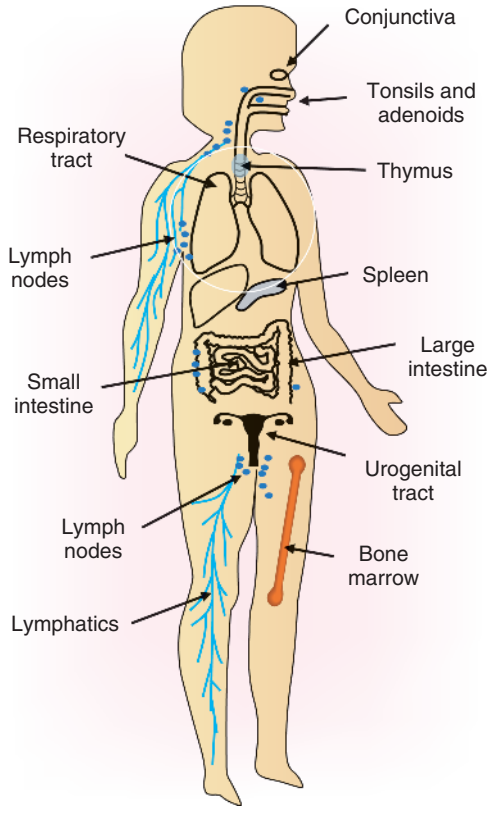

Figure 1.2 Tissues of the immune system.

most risk are the ones that are most frequently exposed to the outside, the most visually obvious tissue being the skin. Other tissues come into direct contact with the outside including the urogenital tract, gastrointestinal tract and the respiratory tract. For example, the lungs sample in the region of 11,000 litres of air every day and with each breath there is the risk of inhaling a harmful substance or potentially pathogenic microbe. Likewise the intestines are constantly exposed to material ingested through swallowing and, in addition, the gut has to cope with the billions of commensal bacteria that reside there. These tissues have therefore developed a series of immunological barriers to prevent infectious disease. The common mucosal immune system and mucosal-associated lymphoid tissue (MALT) are phrases that have been used to describe the composition of the immune system at sites that possess a mucosal lining. The respiratory, gastrointestinal and genital tracts are the major components of the MALT and function as immunological barriers at sites that are exposed to external substances.

Other tissues, which are not classified as mucosal, also contribute to the immune system. Central to haematopoiesis is the bone marrow, which is located within cavities of the long bones and is the site where all cells of the blood are derived. The bone marrow is home to multipotent stem cells that give rise to red blood cells, platelets and all the different types of white blood cell. The thymus is another important organ responsible for the differentiation and maturation of a population of white blood cells known as T cells and is located in the chest cavity just above the heart and surrounding the trachea.

Both the bone marrow and thymus are known as primary lymphoid organs, as these are the sites of immune cell development. There are also secondary lymphoid organs such as the spleen, which is located within the upper left hand quadrant of the abdomen. The spleen is responsible for the removal of moribund red blood cells and the initiation of immune responses directed toward blood borne antigens. Other secondary lymphoid organs include the lymph nodes, which are part of the lymphatic system. Lymph nodes are critical for the proper initiation of many immune responses. They are found throughout the body and are concentrated in regions that drain large body parts such as the neck, thorax and abdomen. They provide sites for the initiation of immune responses to antigens derived from body tissues that have been filtered into lymph nodes via the extensive lymphatic system. The tonsils and adenoids are further examples of organized

secondary lymphoid organs, which play an important role in the initiation of immune responses to pathogens that enter the body through the oral cavity.

The cells of the immune system are sometimes referred to as immunocytes, the most important of which are the white blood cells (otherwise known as leukocytes; from the Greek leuko (white) and cyte (cell)). All leukocytes originate within the bone marrow from precursor stem cells and can be divided into three groups, depending on their ontogeny (Figure 1.3). The first group are the granulocytes, which include neutrophils, eosinophils, basophils and mast cells. The second group are the myeloid cells that include the monocytes, macrophages and dendritic cells (DCs). The third and final group are the lymphocytes that comprise the natural killer (NK) cells, T cells and B cells. This classification is based on developmental lineage, which will be discussed further in this chapter, as a result of a process known as haematopoiesis. However, when studying the immune system it is sometimes more helpful to classify the different cell types in accordance with cell function. To this end the immune system is often divided into the innate immune system and the adaptive immune system (discussed later in the chapter). Alternatively, the immune system can be studied in terms of the type of immune response it generates and can therefore be classified as either being antibody-mediated or cell-mediated (Figure 1.4). These terminologies will be become clearer as we proceed through the subsequent chapters.

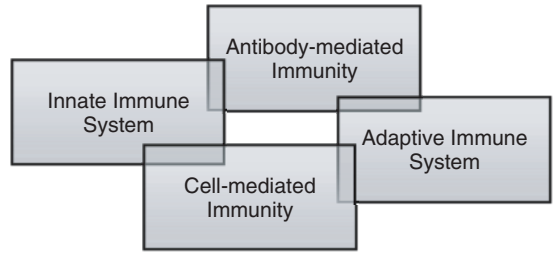

Figure 1.4 The immune system can be compartmentalised based on function. Certain components overlap, although innate and adaptive systems are considered separate.

There are several key concepts that must be addressed when considering how the immune system works. The first is why the immune system exists at all? It can be argued that the immune system has evolved in order to defend our body against invading pathogens. It is therefore important to understand how the immune system is organized in terms of the cell types responsible for orchestrating an immune response and in terms of the tissues that provide an appropriate environment for the generation of an immune response. It is then important to understand how immune responses are initiated and, once active, how these responses are regulated. Finally, it is important to gain an understanding of how the immune system is able to provide us with immunological protection against a pathogen that we have previously encountered, a process known as immunological memory. Some

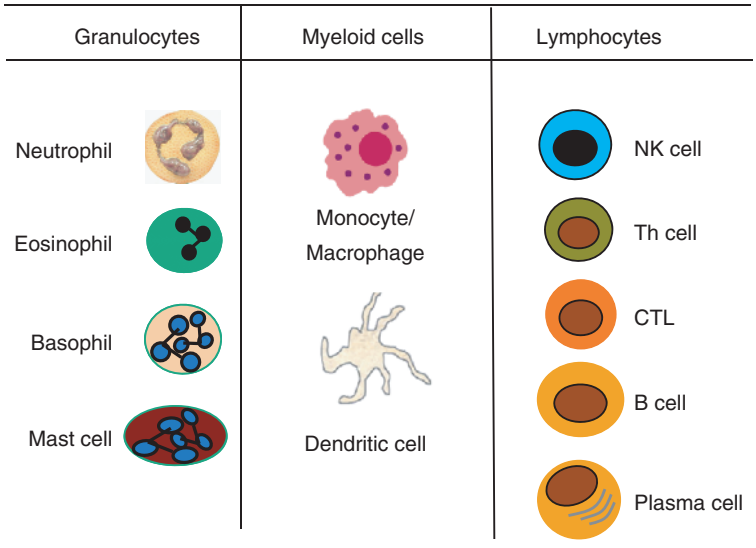

Figure 1.3 Cells of the immune system, which are divided into granulocytes, myeloid cells and lymphocytes.

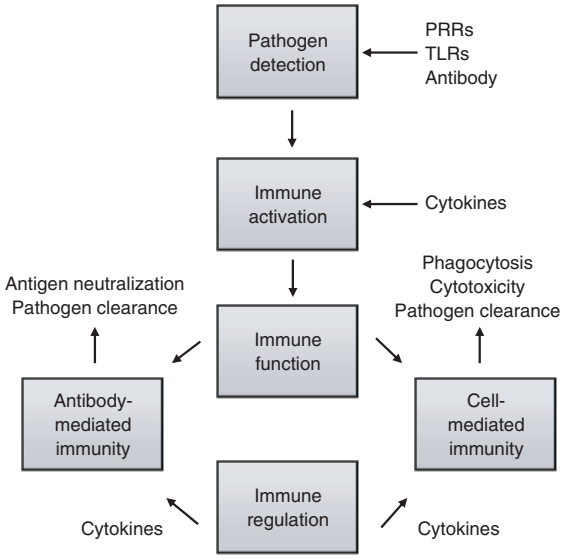

Figure 1.5 Key concepts in the development of an immune response. First pathogens must be detected and recognised as a threat. This pathogen recognition then activates the immune system and results in immune function, which can be divided into antibody-mediated or cell-mediated immunity. The functional activity must then be regulated after the pathogen has been dealt with and is known as immune regulation.

of these key concepts and immunological terms will be introduced in this chapter (Figure 1.5), while subsequent chapters aim to provide detailed descriptions of specific immunological mechanisms.

1.3 Activation, regulation and functions of immune responses

One of the most important concepts in immunology is the recognition of foreign substances by the immune system. For example, microorganisms such as bacteria and viruses produce a multitude of proteins, carbohydrates and glycolipids, which can all be recognized by cellular receptors expressed on the surface of immune cells. The most widely studied family of microbial recognition receptors are known as pattern recognition receptors (PRRs), because they recognize evolutionary conserved molecular patterns produced by microorganisms. The recognition of microbial products, which are known as pathogen associated molecular patterns (PAMPs), is one of the first steps in the activation of an immune response. Numerous cells of the immune system, and also tissue cells such as epithelial cells, express these PRRs. Probably the most ubiquitous family of PRRs are known as the toll-like receptor (TLR) family, which are responsible for the recognition of a host of PAMPs (discussed further in Chapter 2). The recognition of foreign molecules activates immune cells and results in the initiation of an immune response. For these reasons PAMPs are often referred to as danger signals. This is one way in which the immune system is able to discriminate between foreign substances (non-self) and its own molecules (self).

The interaction between immune cells, and indeed between immune cells and tissue cells, can dictate the phenotype, magnitude and duration of an immune response. It is often the case that an individual immune cell relies on signals derived from the extracellular environment in order to become activated or initiate one or more of its effector functions, for example through the recognition of danger signals. A key family of molecules, known as cytokines, play a central role in the initiation and regulation of immune responses (discussed in detail in Chapters 4 and 5). Cytokines are produced from all types of immune cells and from tissue cells such as epithelial cells of the respiratory or gastrointestinal tracts. Cytokines are normally produced and released from a cell in response to an external substance, such as an invading bacteria or virus. The released cytokine then exerts its biological effects on a target cell. For example, an epithelial cell will respond to an invading bacteria and will secrete several cytokines. These cytokines then signal to nearby immune cells and cause a functional response in those immune cells. This response may involve one or more effects including the cell activation, proliferation, migration, further cytokine secretion or initiation of effector functions. There are several families of cytokine including the interleukins, interferons, growth factors and chemokines, all of which provide a network of soluble mediators that regulate the immune response.

Specialized lymphocytes, known as B cells, can also secrete numerous proteins called antibodies, which are found in bodily fluids such as the blood serum and lymphatics. The role of antibodies within the immune system is to recognize and bind to foreign proteins derived from microorganisms. Any protein that can be bound by an antibody is known as an antigen. The interaction between an antibody and an antigen is a key principle in immunology. The binding of an antibody to an antigen has several downstream consequences, including the neutralisation and clearance of the antigen, and the activation of the effector functions of numerous immune cells. Often the word antibody is interchanged with the word

immunoglobulin, as these two terms describe the very same molecule. The functional consequences of antibody and antigen interactions will be discussed further in this chapter and in subsequent chapters. Immune responses generated as a result of antibody and antigen interactions are commonly referred to as antibody-mediated immunity, which can be considered to be part of the humoral immune response. Any immune component that affords protection and is not associated with the cellular fraction of body fluids is considered humoral.

In addition to PRRs, released soluble mediators and antibody, the immune system utilizes a number of specialized cells that participate in cell-mediated immunity. The mechanisms of cell-mediated immunity are largely independent of antibody and other humoral factors (such as complement proteins). Cell-mediated immunity involves the activation of immune cells and the subsequent deployment of cellular effector functions. For example, macrophages and neutrophils participate in cell-mediated immunity by phagocytosing invading pathogens, or infected host cells, and releasing a cascade of antimicrobial products. Phagocytosis is an important process that engulfs foreign substances and microbes and clears them from the body. NK cells and T cells also participate in cell-mediated immunity by recognizing and lysing virally infected cells. This mechanism is known as cytotoxicity, which kills infected or abnormal cells. The cells that are involved in cell-mediated immunity also secrete a number of cytokines, which regulate any ongoing immune response. Historically, cell-mediated immunity has been separated from antibody-mediated immunity or humoral immunity, depending on whether immunological protection can be found in the cellular fraction or the cell free fraction of body fluids, respectively.

Therefore, the key concepts in immunology can be summarized as components that activate immune cells and initiate immune responses, soluble mediators that signal to immune cells and regulate the immune response, components of antibody-mediated immunity (and also other humoral components), and constituents of cell-mediated immunity.

1.4 Innate versus adaptive immunity

Components of the immune system can be conveniently grouped into either the innate immune system or the adaptive immune system (Table 1.1). The innate immune system encompasses all those aspects of non-cellular immunity, including epithelial barrier defence, antimicrobial peptide secretion, chemical barriers and the complement system. The innate immune system also involves aspects of cellular immunity associated with granulocytes (neutrophils, eosinophils, basophils and mast cells), monocytes, macrophages, DCs and NK cells. Cells of the innate immune response are rapidly initiated and are considered to be the first line of cellular defence against invading microorganisms (Figure 1.6). Essentially, innate immune cells provide protective immunity against infectious microorganisms until adaptive immune responses can be initiated.

Table 1.1 Comparison between the innate and adaptive immune systems.

Innate Immune System	Adaptive Immune System
Rapid response (hours)	Delayed response (days)
Non-specific response to conserved molecules	Highly specific response to antigen
Response fixed (not adaptive)	Response adaptive (changes over time)
No immunological memory	Immunological memory
Humoral and cell-mediated components	Humoral and cell-mediated components
Components found in all animals	Only found in jawed vertebrates

The cell receptors expressed by innate immune cells recognize evolutionary conserved molecules derived from invading pathogens or damaged host tissues, for example through the recognition of danger signals. Each of these receptors recognizes the same molecular motifs, irrespective of the cause or progression of an immune response, and is therefore considered to be part of a

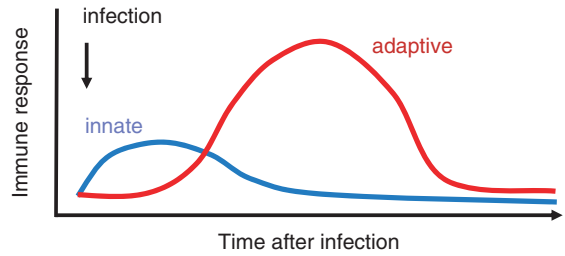

Figure 1.6 Kinetics of a primary immune response. Innate immunity precedes the adaptive immune response.

non-specific response. For example, different bacteria will be recognized by macrophages in much the same way and will activate the same process of phagocytosis. Activation of non-specific innate immune receptors often leads to the development of an inflammatory reaction at the site of tissue damage. This also results in the release of several pro-inflammatory mediators that increase blood vessel permeability, stimulates the migration of more inflammatory cells into the area and is the first step in the activation of the adaptive immune system.

The adaptive immune system takes longer to establish itself and principally involves the T lymphocyte and B lymphocyte populations. Cells of the adaptive immune system are considered to be part of the specific immune response, due to the nature of the receptors that they express. T cell receptors (TCRs) and B cell receptors (BCRs) recognize very specific components of external substances, usually proteins, which are known as antigens. The entire T cell population is thought to consist of as many as 10^9 different T cells, each of which displays a slightly different TCR. Similarly, the number of B cells, each capable of expressing a slightly different BCR, probably exceeds 10^9. Therefore, the adaptive immune system has the capacity to identify a sizeable number of antigens, through the generation of antigen receptor diversity (discussed in detail in Chapter 3). T cells and B cells are therefore part of a highly evolved adaptive immune system that aims to maximize the recognition of as many different pathogens as possible. Furthermore, the mechanisms by which these receptors are produced enable the adaptive immune system to fine tune its response to antigen, so that subsequent responses are more effective. The plasticity built into the generation of antigen receptor diversity has the capacity to alter itself in response to new pathogenic challenges, hence the term adaptive immunity.

Following the stimulation of antigen specific T cells and B cells, a proportion of those cells differentiate into memory cells (Figure 1.7). These memory T cells and B cells are retained within various tissues of the immune system, until they are required at a later time point, when an individual becomes re-infected with the same pathogen. The adaptive immune system is sometime referred to as the acquired immune system, due to its ability to form populations of T cells and B cells that furnish the immune system with immunological memory.

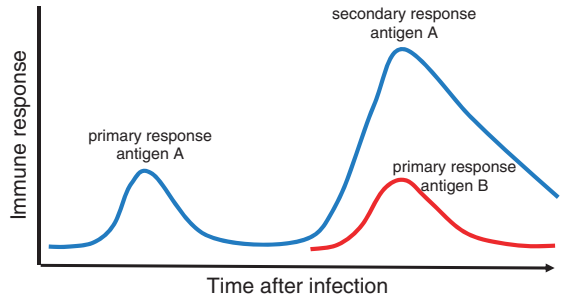

Figure 1.7 Primary and secondary adaptive immune response. Secondary infections with the same pathogen elicits a more rapid and heightened response compared to a primary response.

1.5 Primary and secondary immune responses

The first time that the body encounters a new pathogen a primary immune response is triggered. It usually takes up to 7 days for a T cell response to become established, while it may take as long as 10–14 days for B cells to produce a significant amount of antibody that can be detected in the bloodstream. The reason for such a delay is that neither the B cell nor the T cell population has encountered such an antigen in the past and for this reason these cells are known as naïve B cells or naïve T cells. Therefore, these immune cells require sufficient time to recognize the antigen and start proliferating in order to produce sufficient numbers of antigen-specific clones. In the meantime, while the adaptive arm of the immune system becomes established, the innate immune system plays a vital role in controlling pathogen replication and dissemination. Once fully activated, the adaptive immune system prevents further infection and eventually eliminates the pathogen from the body. The primary immune response is then downregulated so that antigen-specific antibodies become less frequent and T cell numbers return to normal (Figure 1.7).

A secondary immune response occurs when an individual encounters the same pathogen for a second time and principally involves B and T cells of the adaptive immune system. For example, if a person has recovered from influenza infection and encounters the same strain of virus on a subsequent occasion, a secondary immune

response is initiated. A secondary immune response is much quicker in establishing itself than a primary immune response is, because the antigens derived from the pathogen have been encountered before. The magnitude of a secondary immune response is also higher, meaning that more cells participate in the reaction, which results in a much more effective response (Figure 1.7). There is a rapid elevation in antibody levels within the bloodstream, which remain elevated for a longer period of time. This heightened response involves the activation of memory B cells, which can directly differentiate into antibody secreting plasma cells, without having to undergo the various stages of B cell development that a naïve B cell has to undergo. A secondary immune response is also dominated by the production of highly specific antibodies for a particular antigen. The antibodies produced during a secondary immune response are much more specific than those produced during a primary response (Figure 1.8). This is due to a process known as affinity maturation and antibody isotype switching (discussed in detail in Chapter 3), which involves a switch in IgM production to IgG production. Likewise, memory T cells are much more readily activated and they too have a heightening effector response, which is capable of responding more rapidly and with a greater magnitude than during a primary response.

The effectiveness of a secondary immune response relies on the generation of memory B cells and memory T cells (Figure 1.9), which develop following the initiation of a primary immune response. These memory cells reside in various lymphoid tissues throughout the body and contribute to what is known as immunological memory. The term immunity was first used to describe the ability of the immune system to provide protection against infectious diseases and relies on the activation of memory B and T cells. Importantly, vaccination relies on the ability of the immune system to respond more effectively to a secondary encounter with antigen. Many infectious diseases can be prevented by vaccination (Figure 1.10), through the generation of antigen-specific memory cells that become activated in response to a challenge from the real pathogen.

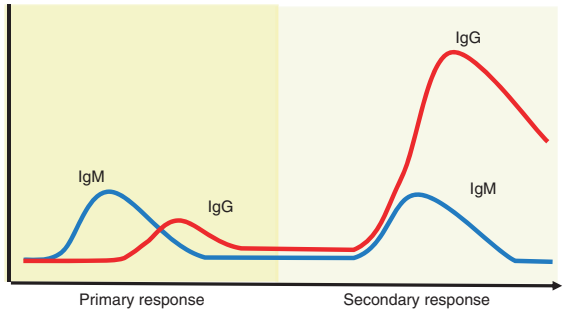

Figure 1.8 Antibody production in primary and secondary immune responses. Primary antibody responses are initially dominated by IgM, while secondary responses are dominated by elevated IgG.

1.6 Immune cell development

Before the array of different immune cells can exert their effector functions and prevent infection, they must first undergo a highly controlled series of developmental stages, collectively known as haematopoiesis. The bone marrow is extremely important for this process and for the continuity of the immune system. It is situated at the centre of all the long bones in the human body and consists mostly of a fatty substance surrounding a stroma of dividing stem cells. The major function of the bone marrow is to produce new lymphoid and myeloid cells, which originate from pluripotent haematopoietic stem cells. In fact, these special stem cells can give rise to any blood cell, hence the term haematopoietic, meaning blood forming. These cells then divide and develop into mature lymphocytes from the lymphoid line or monocytes, dendritic cells and granulocytes from the myeloid line (Figure 1.11). The common myeloid stem cell is also capable of differentiating into red blood cells and platelets. The differentiation of the many cells of the immune system occurs in precise developmental stages and at each of these stages a particular cell lineage is formed. This involves a complicated series of differential gene expression events that subsequently determines the commitment to a certain cell lineage. The genetic potential of a pluripotent haematopoietic stem cell is expansive and it is possible for that stem cell to differentiate into any one of a number of available cell types. As haematopoiesis proceeds, the haematopoietic stem cell becomes more and more specialized and its genetic potential becomes increasingly restricted. This eventually leads to cell fate

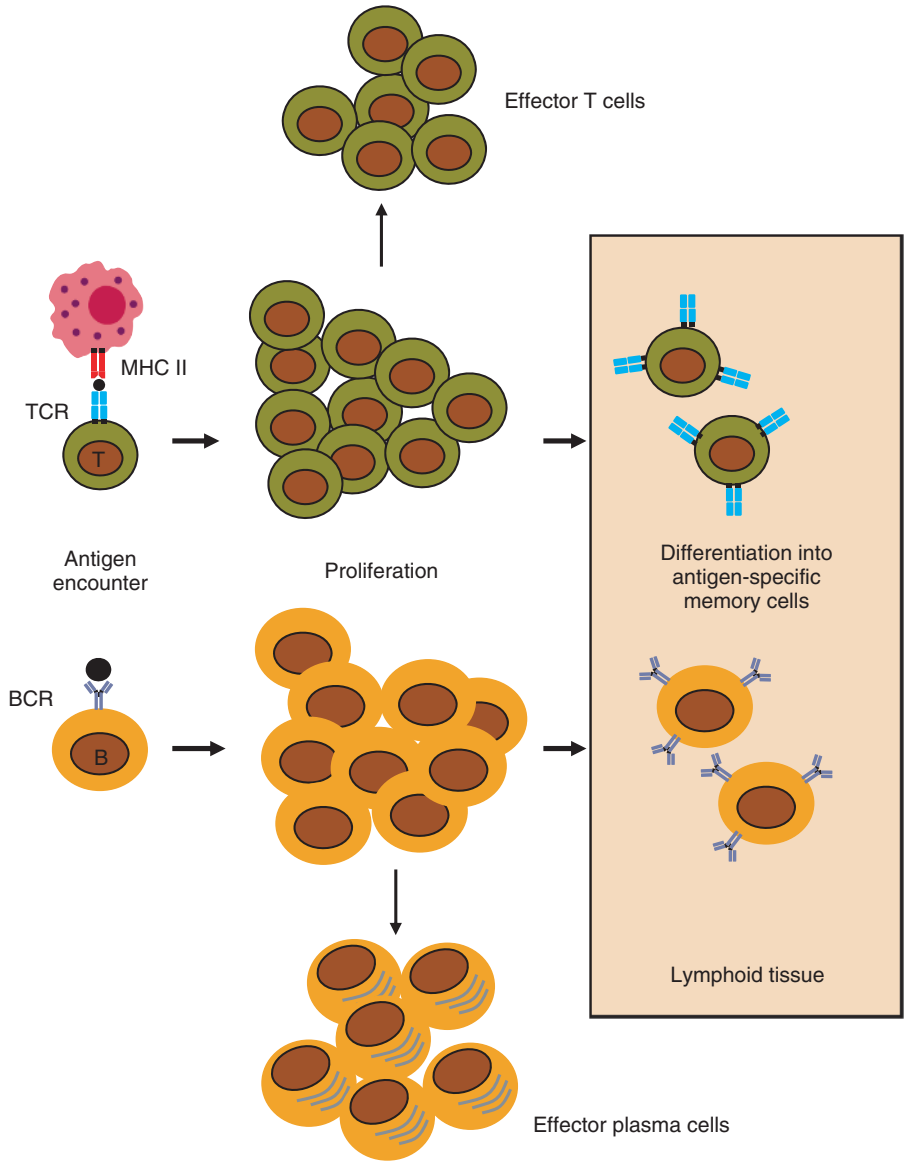

Figure 1.9 Generation of memory lymphocytes. Antigen stimulation leads to lymphocyte differentiation into effector cells. A subpopulation of lymphocytes differentiate into long-lived memory cells.

decisions that are irreversible and forces progenitor cells to continue down a particular cell lineage, for example the lymphocyte lineage.

The haematopoietic stem cell is driven to differentiate into a particular cell lineage based on what signals it receives from the extracellular environment within the bone marrow. One set of signals instructs the stem cell to differentiate into a common lymphoid progenitor cell and the other into a common myeloid progenitor cell. In other words, certain signals favour lymphocyte development, while other signals favour myeloid cell development. The lymphoid progenitor cell is capable of

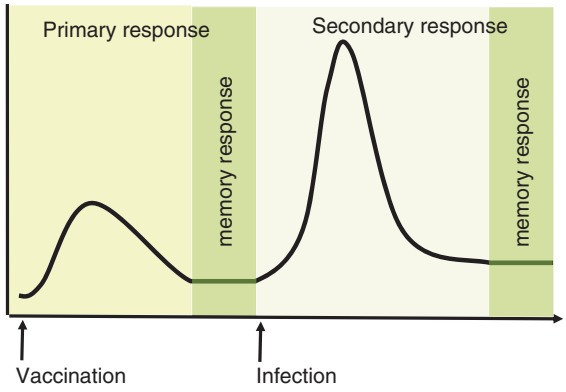

Figure 1.10 Vaccination induces immunological memory. Pathogen-specific memory cells are generated following vaccination. Infection with the wild type pathogen reactivates these memory cells and a rapid and robust secondary immune response follows.

either differentiating into an NK cell precursor, or into a lymphocyte precursor that eventually gives rise to T cells and B cells. Several soluble factors are involved in driving this differentiation. For example, stem cell factor (SCF) is associated with both NK cell precursor and lymphocyte precursor development, while IL-7 signalling is specifically associated with T and B cell differentiation. T cell precursors leave the bone marrow and migrate to the thymus, where the final stages of T cell development take place. This results in the differentiation of immature T cells into either CD4+ T cells or CD8+ T cells. These two specialized T cell subsets will be discussed further in this chapter and extensively in Chapter 3. Following the migration of B cells out of the bone marrow, further B cell maturation takes place in other lymphoid organs such as the lymph nodes, spleen and organized lymphoid follicles associated with MALT. Within these lymphoid structures B cell maturation occurs whereby they mature into antibody secreting plasma cells.

Haematopoiesis also gives rise to all the cells of the granulocyte and myeloid lineages. For instance, the common myeloid progenitor cell can differentiate into erythrocytes, thrombocytes (platelets), granulocytes and monocytes, thereby demonstrating its pluripotent capacity within the haematopoietic system. The precursor cells of erythrocytes (red blood cells) are called reticulocytes, which leave the bone marrow and complete their maturation in the circulation. Myeloid progenitor cells also give rise to megakaryocytes that are the precursors for thrombocytes. The main precursor for all the cells of the granulocyte lineage is the myeloblast, while the main precursor that gives rise to monocytes and macrophages is the monoblast. Mast cells, eosinophils, neutrophils and basophils diverge from the myeloblast lineage via independent precursor cells, while differentiated monocytes can subsequently mature into macrophages, once resident in tissues, or into myeloid DCs. Again, a number of growth factors and cytokines are involved in granulocyte and macrophage differentiation, including granulocyte/macrophage-colony stimulating factor (GM-CSF), G-CSF and M-CSF.

1.7 Mast cells and basophils

Mast cells and basophils are both granulocytes that are capable of rapidly releasing pro-inflammatory mediators into the extracellular environment, through a process known as degranulation. The release of pro-inflammatory mediators is a key process that initiates an inflammatory reaction. Examples of pro-inflammatory mediators include histamine, prostaglandins and cytokines, which will all be discussed in detail throughout the proceeding text. It was once thought that mast cells and basophils belonged to the same cell lineage; the circulating basophils giving rise to the mature, tissue residing mast cell. It is now clear that mast cells are derived from a separate precursor cell in the bone marrow, although they only fully mature once they reach their target organ. Mast cells can be detected in most tissues where they usually reside adjacent to connective tissue. They are also present in mucosal tissues such as the digestive, respiratory and urogenital tracts and the skin. Mucosal mast cells have slightly different characteristics to tissue dwelling mast cells, as they require the help of T cells to become fully activated, while tissue dwelling mast cells do not.

The primary function of mast cells is to provide an early response to the presence of microbial antigens. In order to recognize the presence of microorganisms, mast cells rely on antibodies interacting with their specific antigen. The interaction between an antibody and an antigen is then detected by the mast cells through the expression of a cell surface receptor that recognizes antibody, known as an immunoglobulin Fc receptor (FcR). When enough antigen is present, many antibody molecules cross link several adjacent FcRs. This antigen cross-linking is essential for receptor activation and in turn subsequent mast cell activation, degranulation and release of pro-inflammatory

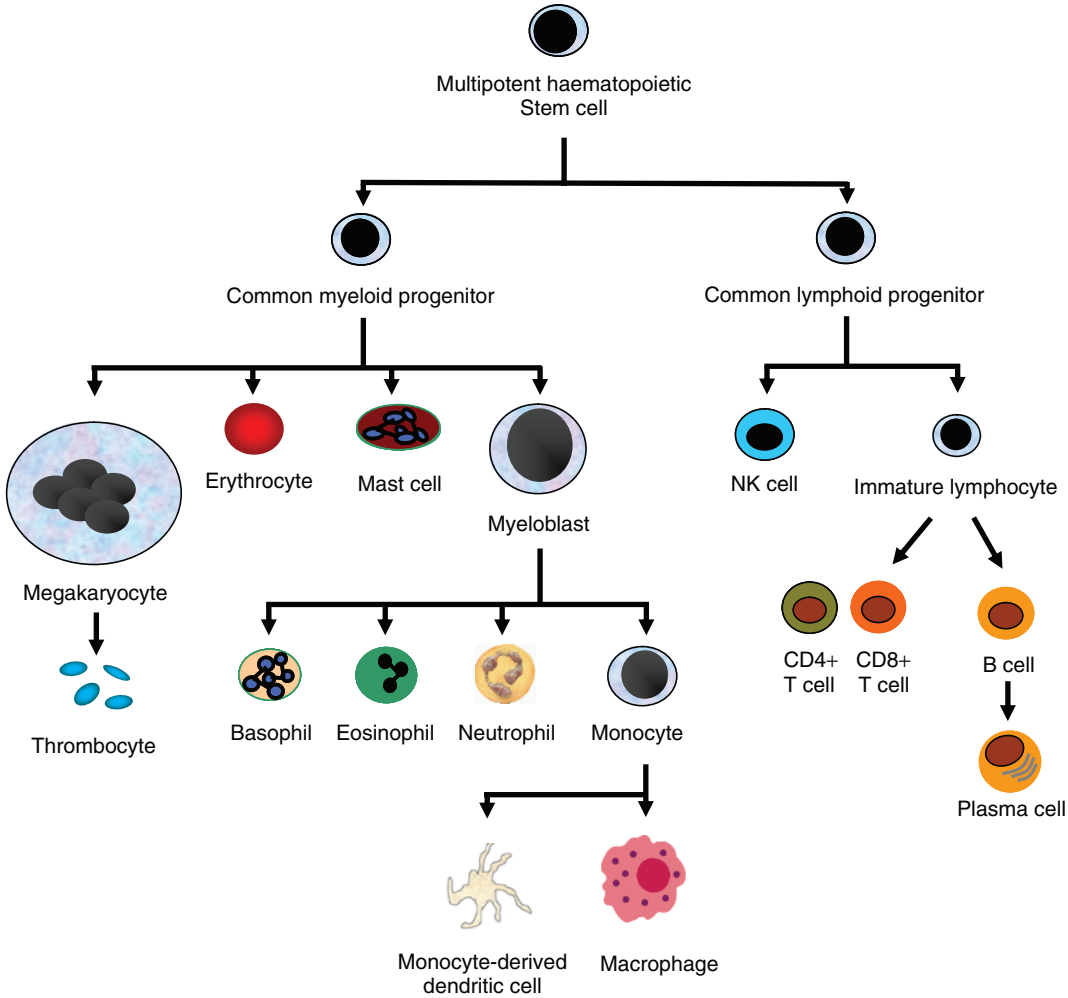

Figure 1.11 Formation of blood cells through the process of haematopoiesis.

mediators. The biological importance of receptor cross-linking should be emphasized, as numerous receptors rely on cross-linking for proper activation. FcR cross-linking on mast cells results the release of an active mediator called histamine, which causes the dilation of blood vessels and stimulates lymphocyte migration into sites of inflammation. Mast cells and histamine have been implicated in the pathology associated with allergic asthma, whereby an allergen (an antigen involved in allergic reactions) cross links FcRs on the cell surface and causes bronchial constriction of the airways. Mast cells also release cytokines and chemokines, which attract eosinophils and other inflammatory cells.

Basophils have a similar function to mast cells and also participate in the release of histamine following FcR cross-linking. Although associated with allergic reactions, basophils and mast cells are thought to have evolved to combat parasitic infections. The degranulation of basophils results in the recruitment of other immune effector cells, following the release of histamine, leukotrines and the cytokine interleukin-4 (IL-4). The cytokine IL-4 is a critical cytokine for the development of T cell responses associated with both parasitic and allergic immune reactions. Although they are the least common of the leukocytes in the blood, basophils can constitute a significant proportion of cells migrating into

sites of allergic inflammation. Therefore basophils, and mast cells, are important cells of the innate immune system capable of an immediate response to an invading pathogen, and are key initiators of subsequent immune responses.

1.8 Eosinophils

Eosinophils are granulocytes that reside in the circulation, MALT and lymphoid organs and are derived from precursor cells in the bone marrow. Under normal homeostatic conditions, they are not frequently observed in healthy mucosal tissues but do increase in number during diseases such as asthma, atopic dermatitis or during helminth infections. The primary function of eosinophils is the release of their granule contents (degranulation), which contain histamine, leukotrines, prostaglandin, reactive oxygen species (including eosinophil peroxidase and superoxide), growth factors and cytokines such as IL-4, IL-5 and tumour necrosis factor (TNF). Eosinophil degranulation therefore induces a local inflammatory microenvironment that attracts other immune effector cells and also results in direct damage to an invading parasite and subsequently to surrounding tissue. A number of factors result in the activation of eosinophils including the cross-linking of FcRs on the cell surface, but also in response to chemokine or cytokine receptor ligation. The chemokines RANTES (regulated upon activation, normal T-cell expressed and secreted) and eotaxin are potent inducers of eosinophil degranulation, while the cytokine IL-5 is important for maintaining eosinophils at sites of inflammation. Eosinophils are also highly phagocytic, particularly in response to antigen-antibody complexes. However, against larger parasites, such as schistosomes, eosinophils rely on the release of reactive oxygen species directly onto the surface of the parasite.

1.9 Neutrophils

Neutrophils are granulocytes that are predominantly found in the blood and may account for as much as 70 per cent of the total circulating leukocyte population. They respond rapidly and effectively to inflammatory signals that originate from sites of infection in tissues, particularly in response to bacterial infection and tissue damage. They are able to exit the circulation through the endothelium of blood vessels and enter sites of inflammation through a process known as chemotaxis. In particular, IL-8 and the complement factor C5a (discussed in Chapter 2) are potent chemotactic factors that recruit neutrophils from the blood and into the area of inflammation. Neutrophils adopt several effector mechanisms that aim to combat the spread of infection or kill the invading pathogen. The first of these is degranulation in response to activation signals such as IL-8 and the cytokine interferon-γ (IFN-γ). Neutrophils release a number of antimicrobial peptides, such as defensins, cathepsins and lactoferrin, which have direct toxic effects on bacteria. In addition, neutrophils release reactive oxygen species and enzymes such as superoxide, hydrogen peroxide, nitric oxide synthase (NOS) and NADPH oxidase, a process known as the respiratory burst that is directly toxic to pathogens and surrounding cells (detailed in Chapter 2). A second effector function is the phagocytosis of bacteria by neutrophils, which places the pathogen inside a phagosome (intracellular vacuole) where more reactive oxygen species are released. Lastly, neutrophils secrete a number of pro-inflammatory cytokines, including IL-12, IFN-γ and TNF, which are involved in the initiation of subsequent immune responses.

1.10 Monocytes and macrophages

Monocytes are derived from the myeloid lineage of haematopoietic stem cells in the bone marrow and constitute approximately 5 per cent of the circulating leukocytes found in the blood. In addition, almost half of all monocytes are stored in the red pulp of the spleen, where they act as a reserve of innate immune cells. In response to infection, monocytes can quickly migrate into tissues where they mature into macrophages or into monocyte-derived DCs. Within tissues, differentiated macrophages are the primary phagocytosing cell of the immune system. They are responsible for phagocytosing a multitude of foreign substances including toxins, macromolecules, cell debris, whole dead cells and microorganisms. Macrophages become active phagocytes following recognition of antibodies or complement factors that stick to the surface of pathogens or infected cells in a process known as opsonisation. Antigens present on the surface of pathogens are opsonized by antibodies, which is enhanced by complement binding to cell membranes. Macrophages are able to recognize these bound antibodies, which signal to the macrophage to induce phagocytosis.

Macrophages are also considered to be professional antigen presenting cells (APCs). The process of phagocytosis involves the digestion and processing of proteins derived from the ingested microorganisms. These proteins are presented on the surface of macrophages and are recognized by T cells. The presentation of antigen by macrophages and recognition of antigen by T cells results in the activation of T cells and the initiation of an adaptive immune response. The process of antigen processing and presentation will be discussed at length in Chapter 3. In addition, activated macrophages are important sources of the pro-inflammatory cytokines IL-1, TNF and IL-12, which are also important in generating adaptive T cell responses.

1.11 Dendritic cells

Dendritic cells (DCs) are derived from precursor cells in the bone marrow and are characterized by a particular morphology involving long cellular extensions known as dendrites. There are several sub-populations of DC, located within different tissues throughout the body, which can be broadly defined as either having a myeloid or lymphoid lineage. Myeloid DCs (mDCs) are thought to be derived from monocytes and can be differentiated from peripheral blood mononuclear cells (PBMCs). Lymphoid-derived DCs are known as plasmacytoid DCs, due to their resemblance to differentiated plasma cells, and are located throughout mucosal tissues. Both populations of DC are professional APCs and are potent activators of the immune system. In particular, mDCs are the most effective APC capable of activating an antigen-specific T cell response. Other DC populations include Langerhan's cells predominantly found in the epidermis of the skin and interstitial iDCs that reside in the dermis of the skin and the stromal compartments of mucosal tissues. However, the distinction between these subsets is often blurred and may reflect patterns of migration or functional specialisations within certain tissue microenvironments.

The primary function of DCs is the presentation of antigen to T cells and the initiation of an adaptive immune response. DCs are often considered to be the critical link between the innate and adaptive immune systems. In addition, they are effective at recognizing the presence of potentially harmful microorganisms through the system of cell surface molecules called pattern recognition receptors (PRRs). These PRRs, including the TLR family, are able to recognize evolutionarily conserved molecular motifs (PAMPs), on the surface of bacteria, viruses, fungi and multicellular parasites. The recognition of foreign substances is a crucial concept in the initiation of any immune response and is often referred to as a danger signal. Without such a danger signal the immune system is not activated, which is how we prevent our immune cells responding to harmless environmental substances or commensal microorganisms. Activation of danger signals through the recognition of PAMPs is one of the first events during an adaptive immune response and results in the release of IL-12 from DCs and migration into regional lymph nodes. The cytokine IL-12 primes T cells for activation, while the architecture of lymph nodes provides an ideal location for antigen presentation to T cells.

Antigen presentation is another fundamental process by which adaptive immune responses are initiated. Exogenous antigen is endocytosed by DCs and processed into small peptides. These peptides are then loaded onto a carrier protein known as major histocompatibility complex (MHC) class II. The processing and presentation of antigen in context with an MHC class II molecule is essential for the initiation of an adaptive immune response. T cells are able to recognize the peptide-MHC complex via its T cell receptor (TCR), which provides the first signal for T cell activation. Antigen presentation by DCs is a central process during the initiation of an immune response and will be discussed at length in Chapter 3.

Another subset of DCs, referred to as follicular DCs (FDCs), resides inside lymphoid follicles within lymph nodes and organized lymphoid structures associated with mucosal sites. They are dendritic in morphology and are responsible for presenting soluble antigen to B cells during B cell development and maturation. However, they should not be confused with mDCs or pDCs as they do not have their origins in the haematopoietic system but rather are derived from mesenchymal cells.

1.12 Natural killer cells

Natural killer or NK cells are members of the innate immune system that are derived from a common lymphoid precursor and are therefore classed as a lymphocyte. However, they do not express TCRs or immunoglobulins like T and B cells do, and therefore their cell receptors do not give them the capacity to adapt to external antigens.

They are known as NK cells due to their potent cellular cytotoxicity against tumour cells and virus infected cells. They are capable of releasing granule components onto the surface of infected cells to induce cell death. NK cell granules contain the cytotoxic proteins perforin and granzyme that induce target cells to undergo apoptosis. There are several mechanisms by which NK cells become activated, including a process known as antibody-dependent cellular cytotoxicity (ADCC). Antibodies that bind to the surface of infected cells are recognized by receptors on NK cells, specifically FcRs that recognize antibody molecules (Figure 1.12). The cross-linking of multiple FcRs activates the NK cell and induces the release of its granule contents. Perforin punches tiny holes in the surface membrane of target cells, while granzyme enters the cell and provokes it to undergo apoptosis.

An alternative means by which NK cells exert their cytotoxicity is through a mechanism known as the recognition of missing self. NK cells express surface receptors that recognize several molecules expressed by host cells. These receptors recognize normally expressed molecules on host cells, which delivers a signal to NK cells that informs them not to kill the healthy cells. This signal is known as an inhibitory signal and is recognized by particular NK cell receptors called killer cell immunoglobulin-like receptors (KIRs). However, when a cell becomes infected with a virus, for example, molecules that are normally expressed on the cell are often downregulated. In effect, this takes away the inhibitory signal from the NK cell and allows the NK cell to exert its cytotoxic functions, thereby killing the infected cell. Therefore, in normal circumstance KIRs recognize molecules on healthy cells and leave them alone. However, when these molecules are downregulated in response to infection, the lack of an inhibitory signal allows the NK cell to initiate effector functions, a term known as the recognition of missing self.

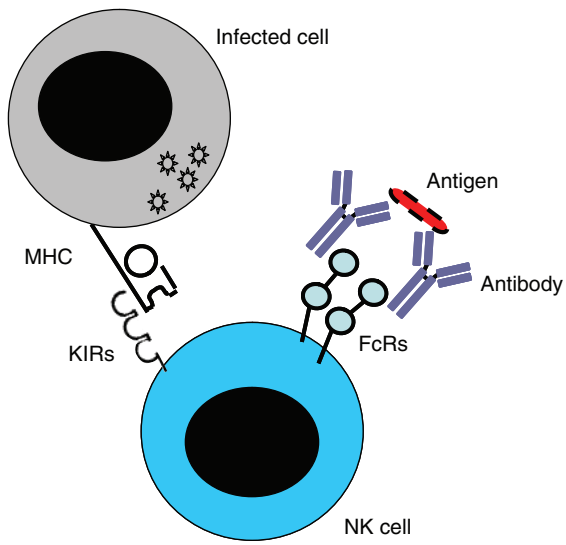

Figure 1.12 Receptor expression on NK cells, which includes killer cell immunoglobulin-like receptors (KIRs) and FcRs. KIRs recognize abnormal expression of MHC molecules on the surface of infected cells, while FcRs bind to cross-linked antibody/antigen complexes.

1.13 CD4+ T helper cells

CD4+ T helper (Th) cells are lymphocytes that originate from the bone marrow but complete their development in the thymus (the name T cell is derived from the stages of thymic development). Thymic development is a critical period for the differentiation of T cells and involves certain selection processes that only allow functional T cells to enter the periphery (positive selection). This selection process also prevents self-reactive T cells from leaving the thymus (negative selection). The details of thymic selection will be discussed in Chapter 3, although it should be noted that T cell selection is another way the immune system discriminates between self and non-self. Thymic selection is important for the prevention of self reactive T cells and the development of autoimmune reactions. The selection process in the thymus ensures that T cells are tolerant to self-antigens. T cell tolerance can be considered to be the opposite of autoimmunity.

Th cells are characterized by the expression of the CD4 molecule, which is a co-receptor for the αβTCR. CD4+ T cells are activated when they recognize a peptide antigen that is bound to the surface of an antigen presenting cell such as a DC or macrophage. In particular, CD4+ Th cells recognize peptide antigen bound to an MHC class II molecule on the APC (Figure 1.13). The function of CD4+ Th cells is to assist with the initiation and activation of other cells of the immune system. They provide the necessary signals for CD8+ T cells to exert their cytotoxic function (discussed in the next paragraph); they interact with B cells within secondary lymphoid organs and induce antibody production and

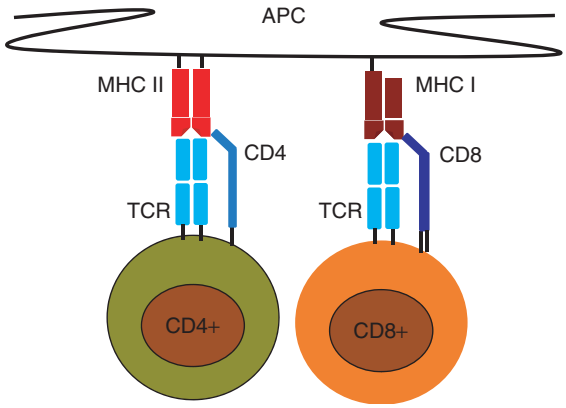

Figure 1.13 CD4+ T helper cells express TCRs that recognize MHC class II molecules, while CD8+ cytotoxic T cells recognise MHC class I molecules. Receptor binding is stabilised by the co-receptors CD4 and CD8.

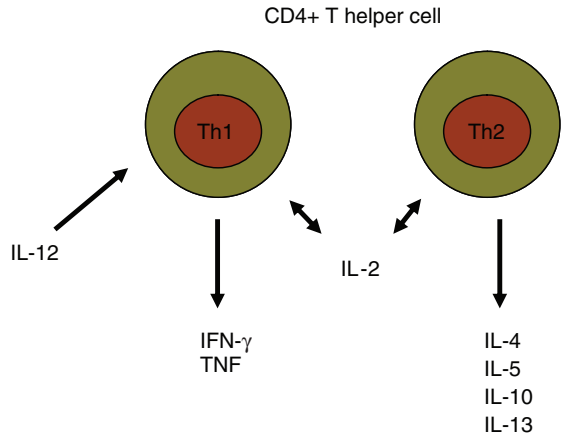

Figure 1.14 Th1 versus Th2 differentiation and cytokine production. IL-12 induces naïve Th cells to differentiate into Th1 cells that express IFN-γ. The lack of IL-12 causes naïve T cells to differentiate into Th2 cells that express IL-4, IL-5, IL-10 and IL-13.

they stimulate macrophage phagocytosis. Therefore, they have acquired the term helper T cell (Th cell). A major part of CD4+ Th cell function is the release of stimulatory cytokines that promote proliferation, differentiation or effector functions. For example, IL-2 is produced by all CD4+ T cells and is important for the proliferation and maintenance of both CD4+ Th cell and other T cell populations.

Depending on which cytokines CD4+ Th cells produce, they can be further differentiated into Th1 and Th2 cells (Figure 1.14). This is a widely used nomenclature that helps to determine the type of immune response that an individual develops. For instance, viral infections tend to induce Th1-type immune responses, while intestinal parasites and allergic reactions are associated with Th2-type immune responses. The reason for possessing different types of immune responses is that each response is better suited to clearing a particular pathogen. Therefore, Th1-mediated immune responses are ideal at fighting intra-cellular viruses, while Th2-mediated immune responses are better at clearing extracellular parasites. The cytokines produced by Th1 and Th2 cells differ (Figure 1.14), so that Th1 cells predominantly express IFN-γ and TNF, while Th2 cells predominantly express IL-4, IL-5, IL-10 and IL-13. The differences in cytokine production by Th cells have a significant effect in the type of immune response that is initiated. Th1 and type-1 cytokines are associated with the development of cell-mediated immunity. For example, they stimulate cytotoxic functions in CD8+ T cells and NK cells and induce macrophages to undergo phagocytosis. On the other hand, Th2 responses are associated with antibody-mediated immunity, enhanced antibody production by B cells and allergic-type reactions.

Another important CD4+ T cell population exists that are known as T regulatory cells (Tregs), which are characterized by the production of IL-10 and transforming growth factor (TGF)-β. Treg cells are responsible for the regulation of immune responses, so that any immunopathological consequences of inflammation are minimized. IL-10 and TGF-β are thought to be the principle immunoregulatory cytokines that act to dampen down excessive immune responses.

In summary, CD4+ T cells can be divided into several sub-populations whose diverse functions are mainly attributed to the cytokines that they produce. They are key mediators of immunity that instruct and orchestrate the pattern of immune cell development and differentiation, either through activation or regulation of the immune response.

1.14 CD8+ cytotoxic T cells

CD8+ T cells are lymphocytes that are commonly known as cytotoxic T lymphocytes (CTLs) due to their cytolytic capabilities against virally infected cells and tumour cells. Like CD4+ Th cells, CD8+ CTLs originate in the bone marrow and differentiate in the thymus. CTLs

also undergo a similar selection process in the thymus, whereby only those CD8+ T cells with a functional αβTCR are allowed to survive (positive selection), while those that are reactive to self antigens undergo apoptosis (negative selection). The CD8 molecule expressed by CTLs acts as a co-receptor with the αβTCR, which specifically recognizes MHC class I molecules expressed on the surface of all somatic cells (Figure 1.13). The recognition of peptide: MHC class I complexes by TCRs on the surface of CD8+ CTLs activates their cytolytic machinery. The cytolytic factors are similar to those released by NK cells and include perforin and granulysin, which have the desired effect of killing virally infected cells through the induction of apoptosis. In addition, CTLs may be able to kill target cells through the surface expression of FasL, which binds to its receptor Fas on the target cell. The ligation of Fas initiates an apoptotic pathway within the target cell, ending in cell death. Therefore, CD8+ CTLs are important lymphocytes that kill infected or abnormal cells.

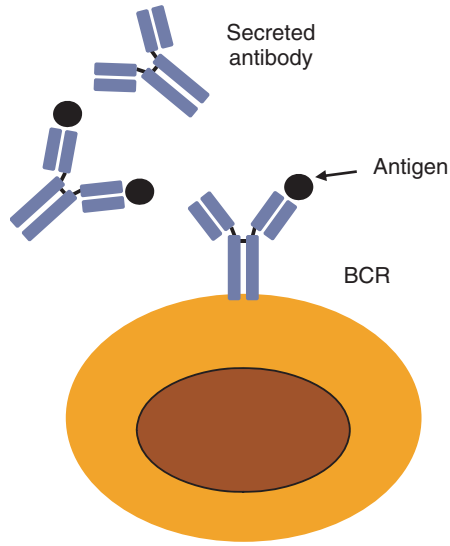

Figure 1.15 Immunoglobulin expression by B cells can take two forms. When bound to the cell surface of B cells it forms part of the B cell receptor complex (BCR). When secreted by plasma cells it is known as antibody. Both bind to antigen.

1.15 B cells

The lymphocytes that are responsible for the production of antibodies are called B cells, so named as they were originally characterized in the avian lymphoid organ the bursa of Fabricius. In most mammals, including humans, B cells are derived from the bone marrow and therefore the nomenclature remains appropriate. The term antibody is also interchangeable with immunoglobulin, which when bound to the surface membrane is known as the B cell receptor (BCR). In general, an immunoglobulin that is secreted by a B cell is known as an antibody, while one bound to the surface of a B cell is known as the BCR (Figure 1.15). B cells that leave the bone marrow continue to mature in the spleen, lymph nodes and secondary lymphoid aggregates of MALT. Each B cell produces antibody that selectively binds to a particular antigen and is known as a B cell clone. Within secondary lymphoid tissues, B cell clonal selection takes place, whereby only those B cell clones that produce antibody with the highest affinity to antigen are preferentially selected. Those B cell clones with low affinity to antigen are deleted. The clonal selection theory is an important concept in immunology that allows a better understanding of how antibody responses are generated. Clonal selection ensures that those antibodies that are selected have the highest possible affinity to an antigen. This favours antigen clearance and the removal of infectious microorganisms from the body.

Mature B cells differentiate into plasma cells that produce significant amounts of secretary antibody. Successful B cell clones also divide and produce more B cells that express antibody of the same specificity, thereby effectively amplifying an antibody response. Antibody production is an important mechanism for the clearance of antigens from the body. This may include the clearance of whole pathogens following antibody binding to antigens on the surface of microorganisms. In addition, B cells can also act as professional APCs under certain circumstances, for example during interactions with CD4+ Th cells within secondary lymphoid tissues.

The majority of antigens recognized by the membrane bound BCR are not sufficient to induce B cell activation alone, but rather secondary signals are required from CD4+ Th cells. The antigens that these B cells recognize are therefore known as T-dependent antigens. On the other hand, some antigens are able to stimulate B cell activation in the absence of T cell help and are therefore known as T-independent antigens. These antigens tend to be formed of multiple repeating units that are able to cross-link BCRs and provide a sufficiently strong signal to induce activation, differentiation and subsequent

antibody secretion. However, it is thought that the vast majority of antigens are T-dependent antigens.

1.16 γδ T cells

Conventional T cells, such as CD4+ Th cells and CD8+ CTLs, express the αβTCR that comprises one α-chain and one β-chain. However, a population of unconventional T cells express a different TCR called the γδTCR, made up of one γ-chain and one δ-chain. Instead of recognizing peptide:MHC complexes, the γδTCR is thought to bind to certain non-classical MHC molecules, which present phosphorylated or lipid antigens rather than normal peptide antigens. γδ T cells are far less common than αβ T cells and are predominantly located in mucosal tissues such as the gut, where they tend to reside in the intra-epithelial compartment. Therefore, they are often known as intra-epithelia lymphocytes (IELs). They possess some characteristics of adaptive immune cells, such as a TCR, while at the same time resemble innate immune cells. Although it is not entirely clear what their precise role is in the immune system, it is thought that they may be important during the early phase of an immune response or as regulatory sub-population of T cells.

1.17 Natural killer T cells

NKT cells represent a small population of T cells that share properties of both NK cells and conventional T cells. The TCRs expressed by the conventional T cell population are highly variable, so that they have the potential to recognize many different peptide antigens. However, the TCRs of NKT cells are far less variable and can only recognize a limited number of antigens, mostly glycolipids. The most characterized population of NKT cells express a restricted αβTCR repertoire that recognizes the non-classical MHC molecule CD1d, and are known as invariant NKT cells (iNKT cells). The functional significance of NKT cells is only just beginning to be appreciated. They are effective producers of IFN-γ, TNF and IL-4 and therefore are capable of contributing to pro-inflammatory signals. However, they may also play a role in regulating the immune system, through the recognition of lipid antigens derived from both pathogens and cellular sources resulting from tissue damage.

Table 1.2 Primary and secondary lymphoid tissues.

Primary lymphoid tissues	Secondary lymphoid tissues
Bone marrow	Spleen
Thymus	Lymph nodes
Bursa of Fabricius (birds)	Peyer's patches (gut)
	Tonsil and adenoids (airways)
	Appendix

1.18 Anatomy of the immune system

The physical structure of the immune system comprises many organs and tissues of the body, from the bone marrow, which is responsible for generating new cells, to the localized lymph nodes where lymphocytes are primed to mount their attacks on invading pathogens. The organs of the immune system can be divided into primary lymphoid organs and secondary lymphoid organs (Table 1.2). The bone marrow and the thymus are examples of primary lymphoid organs, where immune cells are generated and undergo differentiation. Secondary lymphoid organs include the lymph nodes, Peyer's patches and tonsils and are sites where immune responses are initiated. Secondary lymphoid organs are known as inducer sites, because they provide the correct environment for immune responses to be induced. Sites of inflammation or infection, where the actual immune response takes place and where leukocytes exert their biological functions, are known as effector sites. Examples of effector sites might include the dermis of the skin, the epithelium of the intestine or the bronchial lining of the airways. Without the presence of inducer sites, immune responses can not be effectively mounted and therefore secondary lymphoid tissues are crucial for the normal function of the immune system.

1.19 Lymph nodes

Lymph nodes are encapsulated, organized secondary lymphoid tissues that provide the immune system with several important functions. They are situated at various sites throughout the body, often in clusters in the abdomen,

chest, neck, under the arms and in the groin area, and are integrated with the vascular lymphatic system. One function of lymph nodes is the non-specific filtration and accumulation of particulate antigens and microorganisms. Lymphatic fluid that drains from peripheral tissues enters a lymph node via the afferent lymphatic vessels. Within the lymph node any particulate antigens or microorganisms carried within the lymph are deposited, where the phagocytic activity of macrophages removes them from the system. Another important function of lymph nodes is the provision of an anatomical microenvironment where antigen is filtered and presented to lymphocytes by APCs. Lymphocytes and APCs enter lymph nodes via the bloodstream, through specialized capillaries called high endothelial venules. The structure of the lymph node is such that the likelihood of antigen encounter is maximized, thereby providing a greater opportunity for an interaction between an APC, T cell and B cell. Lymphocytes leave lymph nodes via the efferent lymphatic vessels, enter the circulating lymph and eventually rejoin the bloodstream via the large lymph vessels of the thoracic duct or right lymphatic duct. Lymphocytes activated within a lymph node either migrate to peripheral tissues where they exert their effector functions, or they continue to circulate and eventually re-enter another lymph node.

The anatomical organisation of lymph nodes (Figure 1.16) also enables them to function as sites of B cell and T cell activation and proliferation. Most lymph nodes are bean-shaped structures only a few millimetres long but can considerably increase in size and cellular mass following infection. Lymph nodes are encapsulated by a highly collagenous membrane, which is punctuated by afferent lymphatic vessels that bring draining lymph into the lymph node. The inside of a lymph node can be divided into a highly cellular outer layer known as the cortex and a less cellular inner layer called the medulla. Afferent lymphatic vessels drain into sinuses within the cortex, which are channelled toward the medulla region where efferent lymphatic vessels converge and drain lymph away from the node. Blood vessels enter lymph nodes via the medullary cords and form extensive

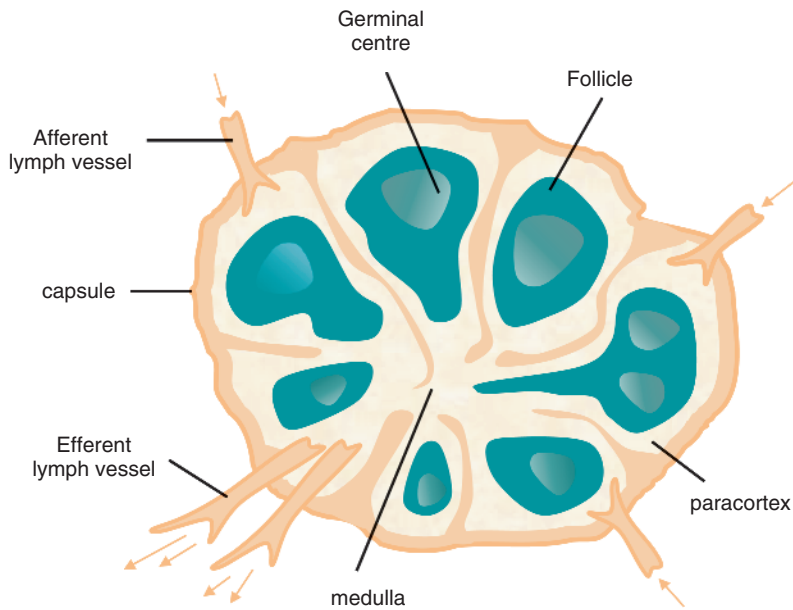

Figure 1.16 Anatomy of a lymph node. A lymph node receives lymph from the afferent lymphatics, while lymph exits a lymph node via the efferent lymphatics. Lymph node architecture consists of T cell areas called the paracortex, which surround B cell areas known as lymphoid follicles. Mature follicles contain germinal centres where B cell differentiation takes place. A central medulla contains migrating lymphocytes.

capillary beds within the cortex. Therefore, the anatomy of a lymph node is such that lymph entering a node via the afferent lymphatics is filtered within the cortex, while lymphocytes enter the cortex in the opposite direction and migrate into areas where antigen is trapped and cells become aggregated. This greatly enhances the chances of a lymphocyte encountering antigen and initiating an immune response.

The outer regions of the cortex contain areas particularly rich in densely packed lymphocytes known as lymphoid follicles, which are in turn surrounded by a less cellular area called the paracortex. The lymphoid follicles represent regions of B cell proliferation, while the paracortex is dominated by proliferating T cells. Although the majority of T cells are located throughout the paracortex, some can also be detected within lymphoid follicles.

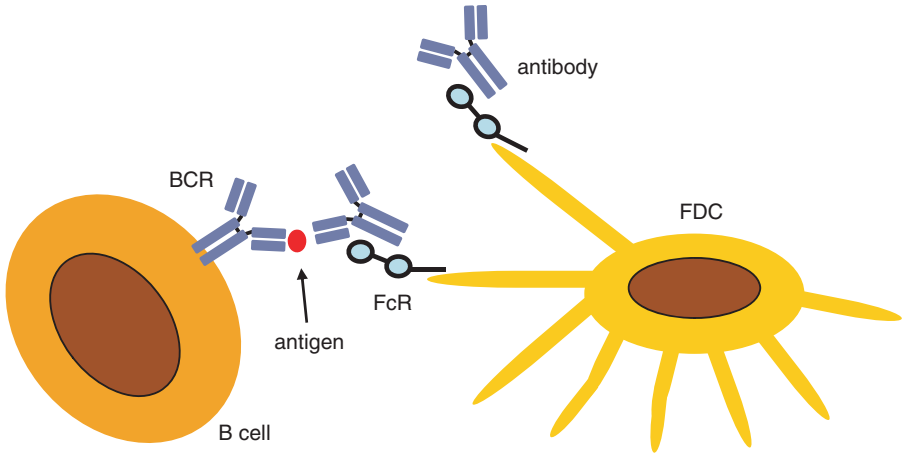

Figure 1.17 Follicular dendritic cells (FDCs) present antigen to B cells in germinal centres. The antigen is bound by pre-existing antibody and attached to FDCs via FcRs. B cell proliferation and maturation requires the presentation of antigen in this way.

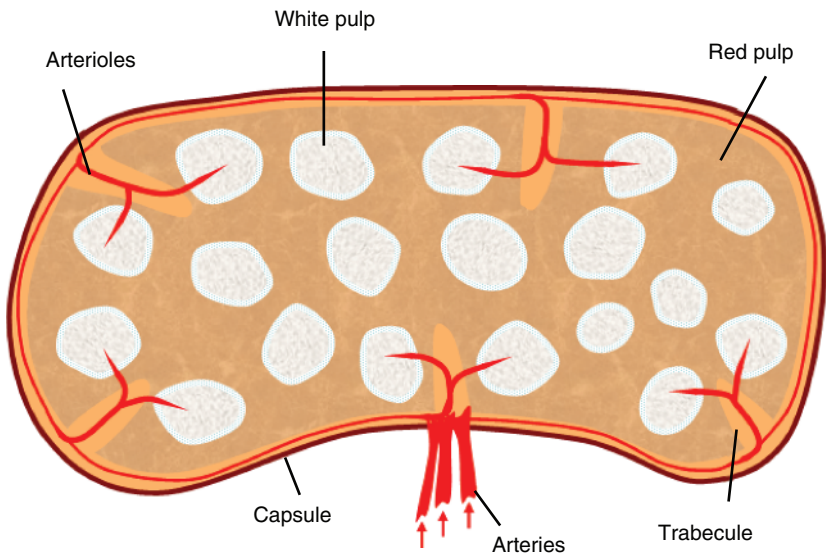

Figure 1.18 Anatomy of the spleen. The spleen consists of a lymphocyte-rich white pulp and a red blood cell-rich red pulp. The spleen receives antigens derived from the blood.

These are thought to be Th cells involved in the activation of B lymphocytes. Within some lymphoid follicles a less dense area of cells can be observed, termed the germinal centre, which is thought to be an area where B cell and T cell interactions take place and where B cell proliferation occurs. Follicles without germinal centres are known as primary follicles, while those with a germinal centre are classified as secondary follicles. Specialized stromal cells also exist within germinal centres called follicular dendritic cells (FDCs), which are responsible for trapping and retaining antigens (Figure 1.17). Presentation of antigen by FDCs induces B cells specific for that antigen to undergo proliferation and start producing antibody. Activated B cells leave lymphoid follicles and migrate through the paracortex into the medulla, where they mature into antibody secreting plasma cells. The medulla is also the site where efferent lymphatic vessels leave the lymph node and eventually drain into the bloodstream via the thoracic duct or right lymphatic duct, thereby transporting activated lymphocytes into the circulation.

1.20 Spleen

The spleen is a large organ of the reticuloendothelial system that functions like a large lymph node, but rather than sampling material from the lymphatic system, the spleen filters components from the blood. It is situated in the upper left quadrant of the abdomen where it receives blood from the splenic artery. Efferent lymphatics within the spleen drain tissue fluid, although no afferent lymphatics are present. Instead blood is drained into the hepatic portal system via the splenic vein. The spleen has two main functions, the first of which is to filter particulate material and defunct red blood cells (erythrocytes) from the blood and second, to provide a site for the initiation of immune responses against antigens derived from the blood. It can be divided into the red pulp and the white pulp, which are responsible for the filtration of red blood cells and the activation of immune responses, respectively (Figure 1.18). Although the primary function of the red pulp is the removal of red blood cells, it also acts as an important reservoir for immature monocytes. The splenic artery branches into arterioles that split into capillary beds that in turn drain into the red pulp sinuses. Within the red pulp sinuses are many macrophages that contribute to the clearance of particulate matter and dying red blood cells. Blood flows into the venous sinuses that give way to larger blood vessels which eventually enter the splenic vein.

Most of the spleen is composed of red pulp, while the white pulp can be divided into the B cell-rich lymphoid follicles and the peri-arteriolar lymphoid sheaths that act as sites for T cell activation. As the splenic artery enters the spleen it branches into many arterioles that drain into the sinuses of the red pulp. Surrounding these arterioles are the peri-arteriolar lymphoid sheaths, although in humans these sheaths are less well defined than in other mammalian species. Nevertheless, large T cell areas are located around arterioles that merge into the red pulp. The B cell-rich lymphoid follicles are situated adjacent to the peri-arteriolar lymphoid sheaths, often where an arteriole branches. Splenic lymphoid follicles also contain germinal centres, which are similar to those within lymph nodes. Certain areas adjacent to arterioles are composed mainly of plasma cells and are also reminiscent of the medullary zone found in lymph nodes. The area of red pulp that immediately surrounds lymphoid aggregations is known as the perifollicular zone. Blood flow through the spleen is much slower within the perifollicular zone, which is thought to maximize the interaction between blood-borne antigen and the lymphocytes present within the spleen.

1.21 Summary

1. The immune system evolved to defend the body against infectious diseases and can be divided into non-specific innate immunity and specific adaptive immunity.
2. The immune system is able to recognize self (its own molecules) from non-self (foreign molecules).
3. Some immune responses are characterized by antibody-mediated immunity, while others are characterized by cell-mediated immunity.
4. An immune response involves a number of key stages: pathogen recognition, activation and initiation, regulation and the generation of immunological memory.
5. All leukocytes (white blood cells) are derived from a process of haematopoiesis in the bone marrow, which gives rise to granulocytes, myeloid cells and lymphocytes.