1

Cells and Organs of the Immune System

Anwarul Azim Akhand and Nazmul Ahsan

Department of Genetic Engineering and Biotechnology, University of Dhaka, Dhaka, Bangladesh

1.1 Introduction

Living animals grow in an environment that is heavily populated with both pathogenic and non-pathogenic micro-organisms. These micro-organisms contain a vast array of toxic or allergenic substances that may be life-threatening. Pathogenic microbes possess a variety of mechanisms by which they replicate, spread and threaten host functions. To counteract this array of threats, the immune system has evolved functional responses using specialised cells and molecules. The immune system is, therefore, a system of cells, organs and their soluble products that recognises, attacks and destroys any sort of threatening entity. By doing so, the immune system primarily protects us from various toxic substances and pathogens. At the same time, it essentially distinguishes dangerous substances from harmless ones. Infiltration with bacterial or viral molecules, for example, can be a dangerous attack on an organism, whereas inhalation of odorant or infiltration of food antigen into the bloodstream is harmless. The destruction of malignant cells is desirable but unnecessary attacks against host tissues are undesirable. Therefore, the cells of the immune system must be capable of distinguishing self from non-self and, furthermore, discriminating between non-self molecules which are harmful or innocuous (e.g. foods).

Two overlapping mechanisms are employed by the immune system to destroy pathogens: the innate immune response and the adaptive immune response. The first is relatively rapid but non-specific and therefore not always effective. The second is slower; it requires time to develop while the initial infection is going on. Although slower, this response is highly specific and effective at attacking a wide variety of microbial pathogens. The detailed mechanism of immune responses is discussed in Chapter 3.

The innate immune system has several first-line barriers that mostly act to limit entry and growth of microbial pathogens. These include physical barriers such as the skin, mucosal epithelia and bronchial cilia. Chemical and biochemical barriers include acidic pH of the stomach and sebaceous gland secretions containing fatty acids, lysozyme and beta-defensins. Once a pathogen overcomes these barriers and gains access to the body, cellular components must come forward to combat the invading organisms.

The immune response to a pathogen depends on sequential and integrated interactions among diverse innate and adaptive immune cells. Innate immune cells mount a first line of defence against pathogens, as antigen-presenting cells communicate the infection to lymphoid cells, which then co-ordinate the adaptive response and generate memory cells that help to prevent future infections. The cells of the innate and adaptive immune response normally circulate in the blood and lymph, and are also scattered throughout tissues and lymphoid organs. The primary lymphoid organs, including the bone marrow and thymus, regulate the development of immune cells from immature precursors. The secondary lymphoid organs – including the spleen, lymph nodes and specialised sites in the gut and other mucosal tissues – co-ordinate the antigen encounter with antigen-specific lymphocytes and their development into effector and memory cells. Blood vessels and lymphatic systems connect these organs, uniting them into a functional whole.

Immunology for Dentistry, First Edition. Edited by Mohammad Tariqur Rahman, Wim Teughels and Richard J. Lamont.

1.2 Hematopoietic Stem Cells: Origin of Immune Cells

Most immune system cells arise from hematopoietic stem cells (HSCs) in the fetal liver and postnatal bone marrow. HSCs are pluripotent cells, i.e. they have the potential to produce all blood cell types. They also have self-renewal capability. Remarkably, all functionally specialised, mature blood cells (erythrocytes, granulocytes, macrophages, dendritic cells and lymphocytes) arise from a single HSC type (Figure 1.1). The process by which HSCs differentiate into mature blood cells is called haematopoiesis. The differentiation of HSCs into various types of immune cells occurs under the influence of cytokines. Two primary lymphoid organs are responsible for the differentiation of stem cells into mature immune cells: the bone marrow, where HSCs reside and give rise to all cell types; and the thymus, where T cells complete their maturation. First, let us focus on the structural features and function of each cell type that arises from HSCs.

1.3 Cells of the Immune System

The immune system may seem like a less substantial entity than the heart or liver; however, immunity collectively consumes enormous resources, producing a large number of cells that it engages for successful function. After being produced from the bone marrow, the immune cells undergo significant secondary education before they are released to patrol the body. Many immune cell types have been identified and extensively studied. Among them, blood leucocytes provide either innate or specific adaptive immunity. They are derived from myeloid or lymphoid lineages. The myeloid lineage produces highly phagocytic cells, including polymorphonuclear neutrophils (PMN), monocytes and macrophages that provide a first line of defence against most pathogens (Table 1.1; see also Figure 1.1). The other myeloid cells include polymorphonuclear eosinophils, basophils and their tissue counterparts – mast cells. They are involved in defence against parasites and in

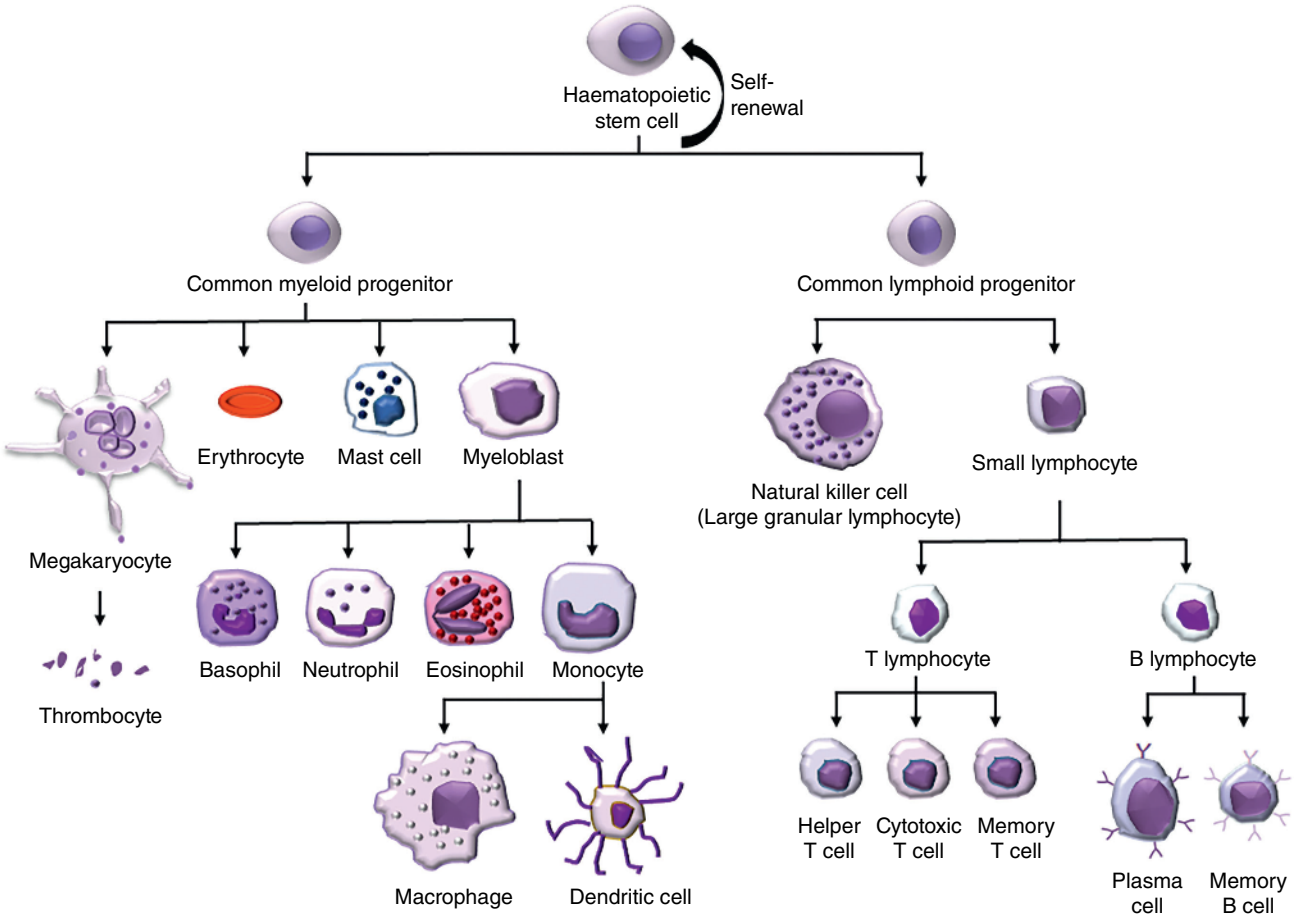

Figure 1.1 Haematopoietic stem cells produce all blood cells by a process of haematopoiesis.

Table 1.1 Myeloid cells and their properties.

Cell	Morphology	Count/L	Function
Neutrophil	PMN granulocyte	2 to 7.5 × 10^9	Phagocytosis and killing of microbes
Eosinophil	PMN granulocyte	0.04 to 0.44 × 10^9	Allergic reactions, defence against parasites
Basophil	PMN granulocyte	0 to 0.1 × 10^9	Allergic reactions
Mast cell	PMN granulocyte	Tissue specific	Allergic reactions
Monocyte	Monocytic	0.2 to 0.8 10^9	Phagocytosis and antigen presentation. Mature as macrophages in the tissue
Macrophage	Tissue specific	Tissue specific	Phagocytosis and antigen presentation
Dendritic cell	Monocytic	Tissue specific	Antigen presentation, initiation of adaptive responses

PMN, polymorphonuclear neutrophils.

allergic reactions. The lymphoid lineage produces cells that are mainly responsible for humoral immunity (B lymphocytes) and cell-mediated immunity (T lymphocytes).

1.4 Cells of the Myeloid Lineage: First Line of Defence

Myeloid cells are the front-line attacking cells during an immune response. Cells that arise from a common myeloid progenitor include erythroid cells such as red blood cells (RBCs) and myeloid cells such as white blood cells (granulocytes, monocytes, macrophages and some dendritic cells). Granulocytes are identified by characteristic staining patterns of 'granules' that are released in contact with pathogens. Granulocytes mainly include neutrophils, basophils and eosinophils.

1.4.1 Neutrophils

Neutrophils are the most abundant of the leucocytes, normally accounting for 50–70% of circulating leucocytes. They have a short life span. They circulate in the blood for 7–10 hours and then migrate to the tissue spaces, where they live only for a few days and do not multiply. During an active infection, the number of circulating neutrophils may increase two- to three-fold. Some neutrophils may remain attached to the endothelial lining of large veins and can be mobilised during inflammation. Neutrophils are about 10–20 μm in diameter and their nucleus is segmented into 3–5 connected lobes; hence they are called polymorphonuclear leucocytes. These cells are highly motile which allows them to move quickly in and out of the tissue during infection. They use their granules to ingest, kill and digest pathogenic micro-organisms. The primary granules include cationic defensins and myeloperoxidase. The secondary granules mostly include iron chelators, lactoferrin and various proteolytic enzymes such as lysozyme, collagenase and elastase. They do not stain with either acidic or basic dyes. The azurophilic granules are mostly lysosomes. Neutrophils dying at the site of infection contribute to the formation of the whitish exudate called pus.

1.4.2 Basophils

Basophils are a type of bone marrow-derived circulating leucocyte. They are also highly granular but with mononuclear appearance and are 12–15 μm in diameter. They account for less than 0.2% of leucocytes, and are therefore difficult to find in normal blood smears. They contain histamine, do not participate in phagocytosis and share many similarities with mast cells. In addition to histamine, basophilic granules also contain various other mediators of inflammation, including platelet-activating factor, eosinophil chemotactic factor and the enzyme phospholipase A. Basophils play roles in the body's response to allergens. They can be activated by antigen/allergen cross-linking of FcεRI receptor-bound IgE. This activation can cause them to release histamine, which is partially responsible for inflammation during an allergic reaction.

1.4.3 Mast Cells

Mast cells are not found in the circulation but exist in a wide variety of tissues, including the skin, connective tissues of various organs and mucosal epithelial tissue of the respiratory, genitourinary and digestive tracts. These cells are mostly indistinguishable from the basophil, but display some distinctive morphological features. They also have large numbers of

cytoplasmic granules that contain histamine and other pharmacologically active substances. Mast cells also play an important role in many inflammatory settings including host defence against parasitic infection and in allergic reactions. When activated by allergens or pathogens, these cells can release wide varieties of inflammatory mediators that take part in inflammatory reactions.

1.4.4 Eosinophils

Eosinophils are polymorphonuclear granulocytes that play roles in host defence against parasites and participate in hypersensitivity reactions. Eosinophil accumulation and inappropriate activation cause pathological asthmatic allergy. Eosinophils make up approximately 2–5% of blood leucocytes in normal individuals and are about 15 μm in diameter, larger than other blood cells like erythrocytes, lymphocytes and basophils. Eosinophils usually have a bilobed nucleus and contain many cytoplasmic granules that are stained with acidic dyes such as eosin. Eosinophil counts may often be raised in people with allergic symptoms as well as in those exposed to parasitic worms. They possess phagocytic activity and destroy ingested microbes.

1.4.5 Mononuclear Phagocytes

Mononuclear phagocytes, which mainly include monocytes, macrophages and dendritic cells, play important roles in both innate and adaptive immunity. Cells of the mononuclear phagocytic system are found in virtually all organs of the body where the local microenvironment determines their morphology and functional characteristics. After development from precursor cells, some monocytes and dendritic cells remain in the circulation, but most enter body tissues. Monocytes are relatively large (10–18 μm diameter), have horseshoe-shaped nuclei with finely granular cytoplasm and a half-life of three days in circulation. They normally make up 5–8% of leucocytes. In tissues, monocytes develop into much larger phagocytic cells known as macrophages, which may differ in appearance and name on the basis of their existing tissue locations. For example, specialised macrophages include Kupffer cells in the liver, Langerhans cells in the skin, glial cells in the central nervous system, alveolar macrophages in the lung and mesangial cells in the kidney (Table 1.2).

The main role of the mononuclear phagocytes is to destroy and remove infectious foreign microbes or dead self-cells (erythrocytes) through phagocytosis (see below). Macrophages are also involved in killing and removing infected cells/tumour cells, secretion of immunomodulatory cytokines and antigen processing and presentation to T cells. Macrophages usually respond to infections as quickly as neutrophils but persist much longer; hence they are more dominant effector cells.

1.4.5.1 The Process of Phagocytosis

Phagocytosis is a type of endocytosis in which a phagocytic cell engulfs a particle to form an internal compartment called a *phagosome*. The cell rearranges its membrane to surround the particle with the ultimate aim of digestion and

Table 1.2 Tissue-specific macrophages and their functions.

Macrophage type	Specific location	Function
Kupffer cells	Liver	Phagocytosis, killing of microbes, hepatic clearance
Langerhans cells	Skin	Participate in immune responses against microbes that invade skin
Glial cells	CNS	Interact with neurons, participate in defence and immune functions
Alveolar macrophages	Lung	Phagocytosis, particle clearance
Mesangial cells	Kidneys	Phagocytosis, cytokine release
Macrophage	Tissue specific	Phagocytosis, interaction with other cells, receptor-mediated endocytosis, release cytokines
Osteoclasts	Bone	Bone remodelling, modulation of immune responses
Splenic macrophages	Spleen	Blood-borne pathogen filtering, culling and pitting of RBCs
Cardiac macrophages	Heart	Regulate cardiomyocyte electrical activity

CNS, central nervous system; RBC, red blood cell.

destruction. The formation of the phagosome triggers acquisition of lysosomes. Phagosomes mobilise and fuse with lysosomes to form phagolysosomes. Within these phagolysosomes, the particles are degraded, destroyed and eventually eliminated in a process called exocytosis. The immune system utilises this process as a major mechanism to remove potentially pathogenic material. A simplified flow chart of the process of phagocytosis is shown in Figure 1.2.

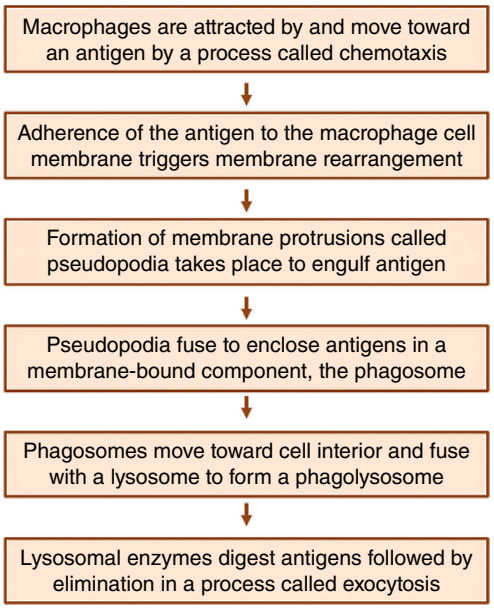

Figure 1.2 Major steps in phagocytosis.

1.4.6 Dendritic Cells

Dendritic cells (DCs) are covered with long membranous extensions that resemble the dendrites of nerve cells. These dendrites extend and retract dynamically to increase the surface area available for browsing lymphocytes and other immune cells. The main function of DCs is to capture antigens in one location and present them to adaptive immune cells in another location. DCs are therefore capable of bridging between innate and adaptive immunity, and are considered excellent antigen-presenting cells (APC). Outside lymph nodes, immature DCs monitor the body for signs of invasion by pathogens and capture invading foreign antigens. They process these antigens intracellularly, migrate to lymph nodes and present the antigen to naive T cells, thus initiating the adaptive immune response. Another category of DCs, known as follicular DCs, also play roles in the maintenance of B-cell function and immune memory.

1.4.7 Erythrocytes and Platelets

Erythrocytes (red blood cells, RBCs) and platelets arise from myeloid megakaryocyte precursors in the bone marrow. RBCs are anucleate biconcave cells in the circulation, which contain haemoglobin and transport body's oxygen and carbon dioxide. They survive around 100–120 days in the bloodstream. Dead RBCs are recycled by the macrophages of the reticuloendothelial system. Although mostly known as oxygen carriers, RBCs are emerging as important modulators of the innate immune response. Haem, the non-protein component of haemoglobin, is capable of generating antimicrobial reactive oxygen species to defend against invading hemolytic microbes. RBCs can also bind and scavenge chemokines, nucleic acids and pathogens in the circulation.

Platelets, also called thrombocytes, are small, colourless cell fragments in the blood that form clots and stop or prevent bleeding. Clot formation is helped by the platelet contents such as granules, microtubules and actin/myosin filaments. Platelets also release inflammatory mediators, thereby participating in immune responses, especially in inflammation. The adult human produces 10^{11} platelets each day. About 30% of platelets are stored in the spleen but may be released when required.

1.4.8 Blood Clotting (Coagulation)

Blood clots are formed by a cascade of complex reactions (Figure 1.3). This process is stimulated by various clotting factors released from the damaged cells (extrinsic pathway) and platelets (intrinsic pathway). Following injury to endothelial cells, platelets adhere to and aggregate at the damaged endothelial surface. Clotting factors cause platelets to become sticky and adhere to the damaged region, forming a solid plug. Release of platelet granule contents results in increased capillary permeability, activation of complement, attraction of leucocytes and bonding between fibrin fibres. Additionally, clotting factors trigger conversion of the inactive zymogen prothrombin to the activated enzyme thrombin. Thrombin in turn catalyses the conversion of the soluble plasma protein fibrinogen into an insoluble fibrous form called fibrin. The fibrin strands form a mesh of fibres around the platelet plug and trap blood cells to form a temporary clot. After the damaged region is completely repaired, the clot is dissolved by an enzyme called plasmin. Clot formation within small blood vessels may also help to fight against pathogenic microbes.

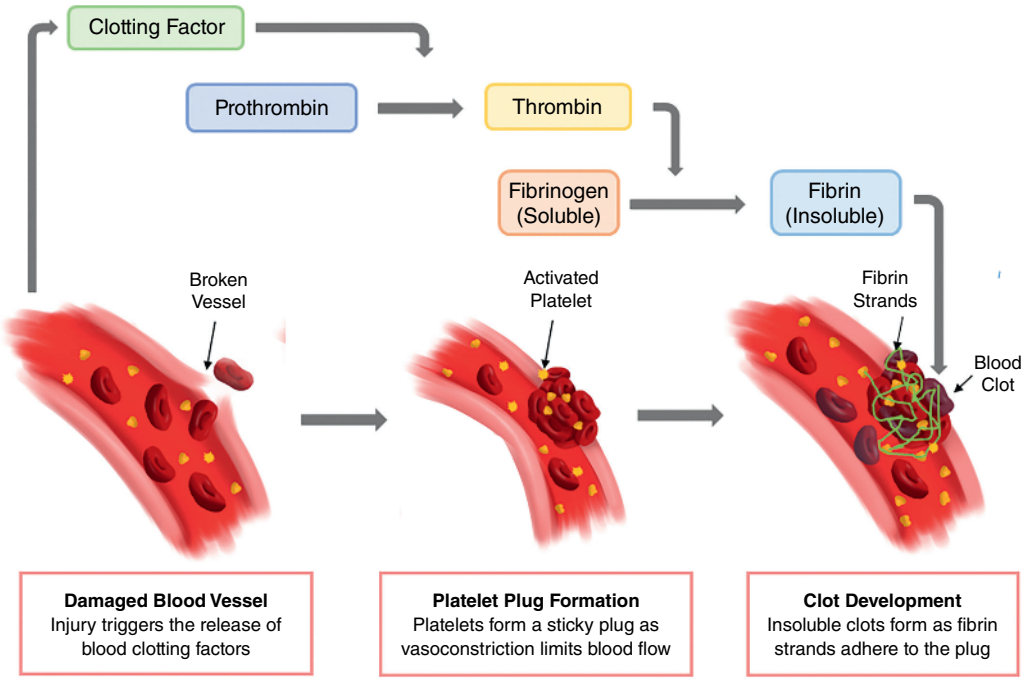

Figure 1.3 Blood coagulation cascade.

1.5 Cells of the Lymphoid Lineage: Specific and Long-lasting Immunity

Lymphoid organs are scattered throughout the body and are mainly concerned with the growth and deployment of lymphocytes. The diverse lymphoid organs and tissues that differ in their structure and function are interconnected by the blood vessels and lymphatic vessels through which lymphocytes circulate. Both the primary (central) lymphoid organs and secondary (peripheral) lymphoid organs are involved in specific as well as non-specific immunity. The blood and lymphatic vessels that carry lymphocytes to and from the other structures can also be considered lymphoid organs. It is also known that the liver can be a haematopoietic organ in the fetus, giving rise to all leucocyte lineages.

Large numbers of lymphocytes are produced daily in the primary lymphoid organs such as the thymus and bone marrow. Some cells then migrate via the circulation into the secondary lymphoid tissues such as the spleen, lymph nodes and mucosa-associated lymphoid tissue (MALT). Lymphocytes represent 20–40% of circulating leucocytes and 99% of cells in the lymph. A healthy human adult has about 2×10^{12} lymphoid cells, and lymphoid tissue as a whole represents about 2% of total body weight.

Lymphocytes differentiate into three major populations based on functional differences: T lymphocytes (T cells) that operate in cellular and humoral immunity; B lymphocytes (B cells) that differentiate into plasma cells to secrete antibodies; and natural killer (NK) cells that can destroy infected target cells. T and B lymphocytes produce and express specific receptors for antigens whereas NK cells do not. In addition, another small group of cells exists, called NKT cells, which are T cells with NK markers (Table 1.3).

1.5.1 T Cells

T cells, responsible mainly for cellular immunity, arise from a lymphoid progenitor cell in the bone marrow. Later, these cells move to the thymus for maturation. The name *T cell* is based on the cell's **T**hymus-dependent development. T cells express a unique antigen-binding receptor called the T-cell antigen receptor (TCR). Cells are selected for maturation in the thymus only if their TCRs do not interact with self-peptides bound to the major histocompatibility complex (MHC) molecules on APCs. Most T cells (90–95%) express the αβ TCR and the rest express γδ TCR. T cells that survive thymic selection become mature and circulate through the peripheral lymphoid organs. Each of these T cells is ready to encounter a specific antigen and thereby become activated. Once activated, the T cells proliferate and differentiate into effector T cells. Some also remain for a longer time as memory T cells.

Table 1.3 Lymphoid cells and their properties.

Lymphocytes	Morphology	Percentage in blood	Function
T cell	Monocytic	70–80	Cell-mediated immunity, immune regulation
B cell	Monocytic	10–15	Antibody production, humoral immunity
NK cell	Monocytic	10–15	Innate response to microbial or viral infection
NKT cell	Monocytic	0.01–0.1	Cell-mediated immunity (glycolipids)

T lymphocytes are divided into two major cell types – T helper (T_H) cells and T cytotoxic (T_C) cells – that can be distinguished from one another by the presence of either CD4 or CD8 molecules on their cell surfaces. These are accessory membrane glycoproteins capable of working as co-receptors. Every T cell also expresses CD3, a multi-subunit cell signalling complex that is non-covalently associated with the TCR. This TCR/CD3 complex specifically recognises antigens associated with the MHC molecules on APCs or infected target cells. In addition to T_H and T_C cells, there is another small group of cells called T regulatory (T_{REG}) cells.

1.5.1.1 T_H Cells (CD4 T Cells)

T_H cells have a wider range of effector functions than T_C cells and can differentiate into many different subtypes, such as T_H1, T_H2 and regulatory T cells. APCs, which express MHC class II molecules on their surfaces, present peptide antigen to T_H cells and thereby these cells become activated. The T_H cells may activate various other immune cells, release *cytokines* and assist B cells to produce antibodies. In this way, they help to activate, shape up and regulate the adaptive immune response.

1.5.1.2 T_C Cells (CD8 T Cells)

T_C cells, on the other hand, kill the infected target cells by releasing their cytotoxic granules. Cytotoxic T cells recognise specific antigens, such as viral fragments presented by *MHC class I* molecules on APCs. In this regard, CD8 co-receptor molecules on the T_C cells help to interact with APCs through their MHC class I molecules. T_C cells require several signals from other cells such as DCs and T_H cells to become activated. T_C cells mainly kill virally infected cells, but are also capable of killing tumour cells and bacteria-infected cells.

1.5.1.3 T_{REG} Cells

T_{REG}s are T cells which have a unique role in regulating or inhibiting other cells in the immune system. These regulatory cells may arise during T-cell maturation in the thymus (natural T_{REG}), but can also be induced during an immune response in an antigen-dependent manner (induced T_{REG}). T_{REG}s control the immune response to self and foreign antigens and help prevent autoimmune disease. T_{REG} cells are also capable of playing a role in limiting our normal T-cell response to pathogens.

1.5.1.4 Memory T Cells

Memory T cells are formed following an infection. These cells are antigen specific and long-lived; they may survive in a functionally quiescent state for months or years presumably after the antigen is eliminated. This survival basically does not need any antigen stimulation. As the memory T cells underwent training previously to recognise a specific antigen, they trigger a faster and stronger immune response soon after encountering it. Memory T cells may either be $CD4^+$ or $CD8^+$. They can be identified by their expression of surface proteins that distinguish them from naive and recently activated effector lymphocytes. Understanding the origins and functions of memory T cells may help in designing and developing vaccines.

1.5.2 Natural Killer Cells

Natural killer (NK) cells are lymphocytes that are closely related to B and T cells. NK cells constitute 5–10% of lymphocytes in human peripheral blood. They do not express antigen-specific receptors such as the TCR/CD3 complex. Instead, they express a variety of killer immunoglobulin-like receptors that are capable of binding MHC class I molecules as well as

stress molecules on target cells. After binding, either a positive or a negative signal is generated for NK cell activation. NK cells are best known for killing virally infected cells as well as detecting and controlling early signs of cancer. NK cells induce death of the infected cells via delivery of apoptotic signals mediated by perforins, granzymes and tumour necrosis factor alpha.

1.5.2.1 Natural Killer T Cells

Natural killer T (NKT) cells belong to T lineage cells that share morphological and functional characteristics with both T cells and NK cells. Characteristically, these cells express CD3 and have a unique αβ TCR. NKT cells are found in low numbers in every tissue where NK and T cells are found. Following activation, NKT cells can release cytotoxic granules that kill targets. They can also immediately release large quantities of cytokines that can both enhance and suppress the immune response. The rapidity of their response makes NKT cells important players in the very first lines of innate defence against some types of bacterial and viral infections. These cells appear to have roles in inhibiting the clinical symptoms of asthma, but also may inhibit the development of autoimmunity and cancer.

1.5.3 B Cells

B cells are considered one of the most important immune cells of the body. Their letter designation (B cell) came from their site of maturation – in the **B**ursa of Fabricius in birds and in **B**one marrow in most mammals. These cells express immunoglobulins on the cell surfaces, where the embedded immunoglobulins act as specific B cell antigen receptors (BCR). B cells constitute about 10–15% of the circulating lymphoid pool. They play a vital role in the adaptive immune response by producing antibodies and presenting antigens to T cells. The activation of B cells is mostly dependent on antigen exposure. Mature B cells can have $1–1.5 \times 10^5$ immunoglobulin receptors for interacting with antigens. Once specific antigens bind to the BCR, the B cells become activated and differentiated into plasma cells that produce and secrete antibodies. Some of the activated cells remain as memory B cells.

1.5.3.1 Plasma Cells

When activated, B cells differentiate into plasma cells which are important for their extended lifespan as well as their ability to secrete large amounts of antibodies. Specific antibodies against an antigen continue to be produced until the infection is controlled. Plasma cells are relatively larger in size and have vast quantities of RNA, which is used for antibody synthesis. Antibodies produced by a plasma cell are of single specificity and immunoglobulin class. Plasma cells are infrequent in the blood, comprising less than 0.1% of circulating lymphocytes, but they are relatively abundant in the secondary lymphoid organs and tissues as well as the bone marrow.

1.5.3.2 Memory B Cells

When activated, some B cells may also differentiate into memory B cells. These usually remain within the body to respond more rapidly in the event of a subsequent infection. Memory B cells are a classic example of immune memory that shows its vigorous antibody response after rechallenge with the same infectious agent. During this type of recall response, reactivated memory B cells can differentiate into antibody-secreting plasma cells which then produce a faster, larger and higher-avidity antibody response. Memory B cell survival is independent of the presence of cognate antigen. The life span of memory B cells may vary. Some human memory B cells can be detected for decades, as in the case of smallpox-specific memory cells. However, in other cases such as in B cell memory response to influenza virus, the memory cell population declines quickly after infection.

1.6 Lymphoid Tissues and Organs

The immune cells are organised into tissues and organs in order to perform their functions most effectively. The structurally and functionally diverse lymphoid tissue and organs are interconnected by blood vessels and lymphatic vessels through which lymphocytes circulate. As mentioned earlier, lymphoid organs are divided broadly into central or primary lymphoid organs and peripheral or secondary lymphoid organs. Lymphocytes develop within the primary organs such as the thymus and bone marrow (Figure 1.4). The secondary lymphoid organs such as spleen, lymph nodes and related lymphoid tissues trap and concentrate antigens. These sites then provide opportunities for the circulating

immune cells to contact with the antigens to initiate specific immune reactions.

1.6.1 Primary Lymphoid Organs

Primary lymphoid organs are the major sites for lymphopoiesis. Lymphocyte differentiation, proliferation and maturation take place in these organs. T cells mature in the thymus and B cells in the bone marrow. During maturation in the primary lymphoid organs, the lymphocytes acquire antigen receptors to recognise and fight against invading antigens.

1.6.1.1 Bone Marrow

Bone marrow is a soft, spongy substance found inside the hard cover of the bones. This spongy marrow is packed full of cells. All the cells of the immune system are initially derived from the bone marrow through haematopoiesis. During fetal development, haematopoiesis occurs initially in the yolk sac and later in the liver. However, after birth this function is gradually taken over by the bone marrow. The adult bone marrow gives rise to granulocytes, NK cells, DCs, B cells, precursor T cells, RBCs and platelets. Various cytokines play roles in the process of differentiation, proliferation and maturation of the cells. Once mature, the cells proceed through the sinusoidal passage from the bone marrow into the blood circulation and other tissues (Figure 1.5). Although the bone marrow is considered a primary lymphoid organ, facilitated entry of circulating leucocytes from peripheral tissue enables it to serve as a secondary lymphoid organ as well.

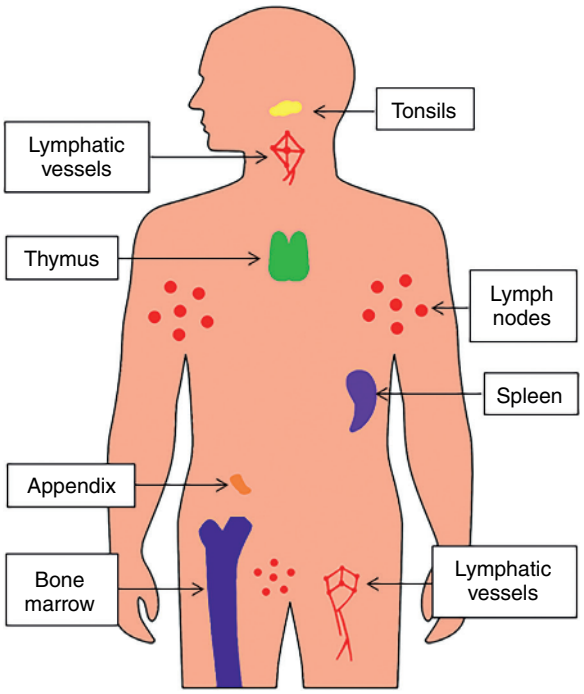

Figure 1.4 Organs and tissues of the immune system.

1.6.1.2 Thymus

The thymus is a lymphocyte-rich, bilobed, encapsulated organ located above and in front of the heart. The size and activity of the thymus are maximal in the fetus and in early childhood. It then undergoes atrophy at puberty although it never totally disappears.

The two thymic lobes are surrounded by a thin connective tissue capsule. Connective tissues around the thymus, called *trabeculae*, divide thymus into lobules containing cortex and medulla regions (Figure 1.6). Hassall's corpuscles are a characteristic morphological feature located within the medullary region of the thymus. There is a network of epithelial cells throughout the lobules, which plays a role in the differentiation process from stem cells to mature T lymphocytes. Precursor T lymphocytes differentiate to express specific receptors for antigen. The cortex contains immature lymphocytes, and more mature lymphocytes pass through the medulla, implying a differentiation gradient from the cortex to the medulla.

The principal function of the thymus gland is to educate T lymphocytes to differentiate between self and non-self antigens. After immature T cell precursors reach the thymus from the bone marrow, they gradually generate antigen specificity, undergo thymic education and then migrate to the peripheral lymphoid tissues as mature T cells.

1.6.2 Secondary Lymphoid Organs

The secondary or peripheral lymphoid organs provide localised environments where lymphocytes recognise foreign antigen and mount a response against it. The spleen and lymph nodes are the major secondary lymphoid organs. Additional secondary lymphoid organs include the mucosa-associated lymphoid tissue (MALT). Examples of MALT include tonsils and Peyer's patches. All secondary or lymphoid organs serve to generate immune responses and tolerance.

1.6.2.1 Spleen

The spleen is situated in the upper left quadrant of the abdominal cavity behind the stomach and close to the diaphragm. It is a large, ovoid secondary lymphoid organ that plays a key role in mounting immune responses against antigens. The spleen functions as a filter for blood, and the filtration is aided by two main microenvironmental compartments in splenic

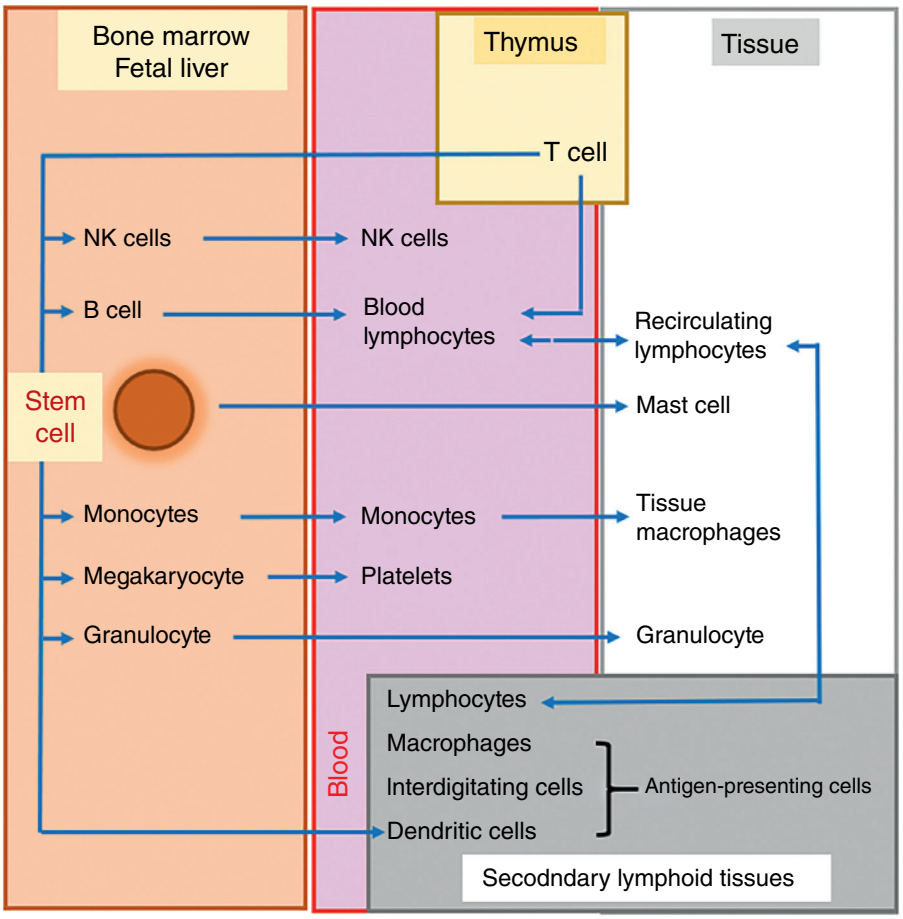

Figure 1.5 Migration of immune cells to different tissues/organs. Immune cells, derived from stem cells in the bone marrow, migrate to different tissues and organs. B cells mature in the bone marrow in adults, whereas T cells mature in the thymus. Lymphocytes recirculate through secondary lymphoid tissues. Tissues/organs are shown in different shading.

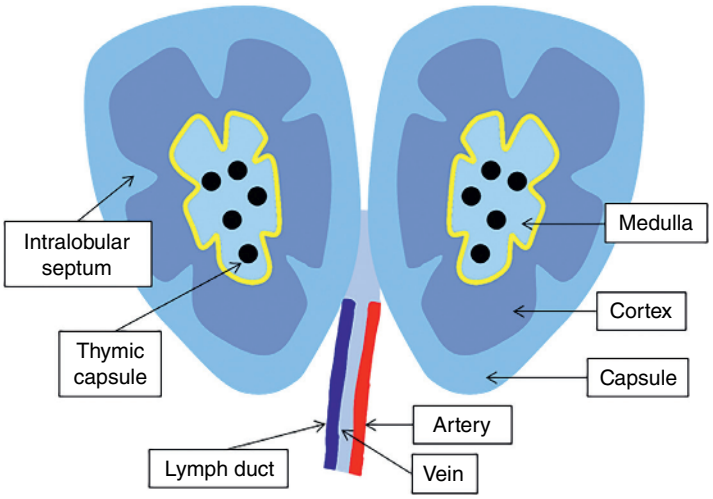

Figure 1.6 Schematic illustration of the thymus.

tissue: the red pulp and the white pulp (Figure 1.7). The red pulp is made up of a network of sinusoids containing large numbers of macrophages, RBCs and some lymphocytes. It is actively involved in the removal of dead RBCs and infectious agents. The white pulp consists of periarteriolar sheaths of lymphatic tissue, and is composed of T- and B-cell areas and follicles containing germinal centres. These follicles are the centre of lymphocyte production, composed mainly of follicular dendritic cells (FDC) and B cells. The germinal centres are where B cells are stimulated by antigens to become plasma

cells that produce and secrete specific antibodies. Every day, approximately half of the total blood gets filtered through the spleen where lymphocytes, DCs and macrophages survey for evidence of infectious agents. The spleen thus serves as a critical line of defence against blood-borne pathogens.

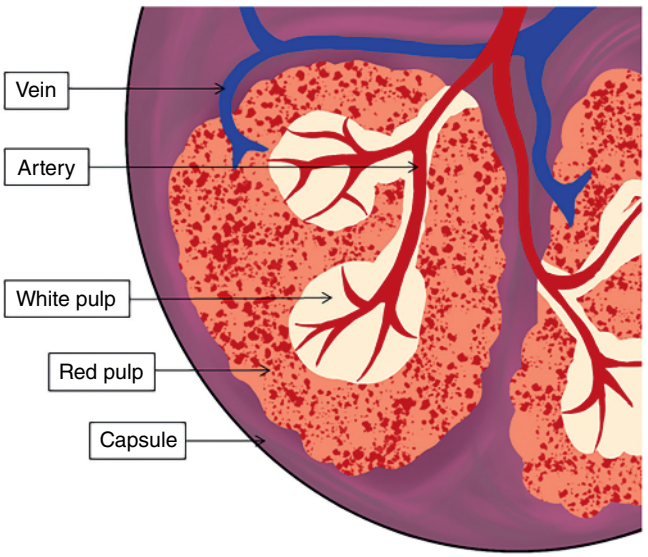

Figure 1.7 Schematic illustration of a portion of the spleen.

1.6.2.2 Lymph Node

Lymph nodes are small solid structures situated at strategic positions throughout the body along the lymphatic system. They are found clustered in strategically important places such as the neck, axillae, groin, mediastinum and abdominal cavity. Human lymph nodes are 2–10 μm in diameter, spherical in shape and encapsulated (Figure 1.8). Each lymph node is surrounded by a fibrous capsule, which extends inside the node to form trabeculae. Lymph enters a node through numerous afferent lymphatic vessels that drain lymph into the marginal sinus. The lymph flows through the medullary sinus and leaves through efferent lymphatics. The lymph nodes filter antigens from the lymph during its passage from the periphery to the thoracic duct. Each lymph node is divided into an outer cortex, inner medulla and intervening paracortical region. The lymph nodes contain both T and B lymphocytes and are primarily responsible for mounting immune responses against foreign antigens. The lymph nodes may be enlarged following antigenic stimulation.

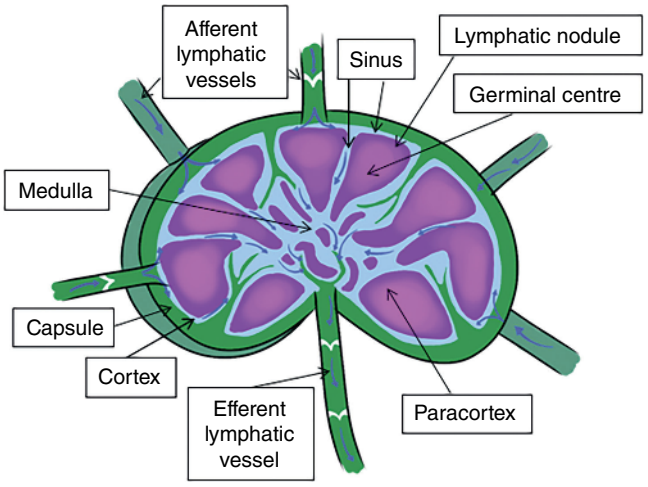

Figure 1.8 Schematic illustration of a lymph node.

1.6.2.3 Mucosa-Associated Lymphoid Tissue

Mucosa-associated lymphoid tissue (MALT) is scattered along the mucosal linings and constitutes the most extensive component of human lymphoid tissue. More than half of the total lymphoid tissue in the body is found associated with the mucosal system. These surfaces are therefore capable of protecting the body from an enormous variety and quantity of antigens.

The most common examples of MALT are the tonsils, Peyer's patches within the small intestine and the vermiform appendix. Location-wise, MALT can be referred to more specifically as gut-associated lymphoid tissue (GALT), bronchial/tracheal-associated lymphoid tissue (BALT) and nose-associated lymphoid tissue (NALT). Tonsils are clusters of lymphatic tissue under the mucous membrane lining of the nose, mouth and throat. Lymphocytes and macrophages in the tonsils provide protection against pathogens that enter the body through the respiratory tract. Similar to tonsils, some non-encapsulated lymphoid nodules are present in the ileum of the small intestine, called Peyer's patches. They play an important role in defending against pathogenic substances that enter the gastrointestinal system.

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