Physiology of red and white blood cells

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Abstract

Blood is made up of plasma and formed elements, which are red blood cells, white blood cells and platelets. The red blood cells (erythrocytes) make up the vast majority of the cells present in the blood. Their principal function is the transport of oxygen from the lungs to the tissues and the transport of carbon dioxide from those tissues back to the lungs. This is due to the presence of haemoglobin, a protein that binds easily and reversibly with oxygen. The affinity of haemoglobin for oxygen changes under certain conditions allowing increased offloading of oxygen at the respiring tissues as required. White blood cells (leucocytes) form the body's defence against invading pathogens. They can be subdivided into granulocytes and agranulocytes, which have different mechanisms of attack against those pathogens.

Keywords Carbon dioxide; erythrocytes; haemoglobin; leucocytes; lymphocytes; macrophages; neutrophils; oxygen

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article, you should be able to:

- describe the structure and function of haemoglobin
- understand the oxygen dissociation curve and the factors affecting it
- describe the different subtypes of leucocyte
- explain the roles of the different leucocytes and how they combat pathogens

Blood is composed of cells and plasma. Red blood cells, white blood cells and platelets form the cellular components. The primary function of blood is to deliver oxygen to the tissues and remove carbon dioxide and waste products. Other important roles include those of immunity and defence, homeostasis and haemostasis. This article concentrates on the physiology of red and white blood cells.

Red blood cells

Structure and function

Red blood cells (erythrocytes) are the most numerous cellular component in blood accounting for approximately 94% of cells. This equates to a cell count of 4.6–6.1 $\times 10^{12}$/l in men and 4.2–5.4 $\times 10^{12}$/l in women. They are biconcave discs in shape that, by the time they enter the circulation, have no nucleus nor organelles. They are 6.5–8.5 μm in diameter and 1.5–2.5 μm thick. This unique shape gives them a large surface area to facilitate gas exchange and also reversibly deforms to allow passage through the capillary beds. The average life span of the red blood cell in the circulation is 120 days.

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The red cell membrane is a lipid bilayer comprised of 50% protein, 40% lipid and 10% carbohydrates. The carbohydrates on the outer surface of the membrane are glycoproteins and glycolipids responsible for the antigenic identity of the cells and have a role in ABO compatibility.

An erythrocyte requires energy to maintain its shape and to maintain the iron contained within it in the reduced (ferrous) state. ATP is produced within the cell via the Embden-Meyerhof pathway and NADPH by the hexose monophosphate shunt (details of which are beyond the scope of this article).

The main functions of erythrocytes are:

- to transport haemoglobin (Hb) which carries oxygen from the lungs to the tissues
- allow carbon dioxide to be transported from the tissues to the lungs predominantly in the form of bicarbonate
- facilitate acid base balance - Hb is an excellent acid-base buffer,

Life cycle – haematopoiesis and sequestration

All blood cells are produced in red bone marrow. This is active cellular marrow present in all bones in children but that by the age of 20 years is predominantly found in flat bones and the proximal portions of the humerus and femur. In the fetus, bloods cells are also produced in the liver and spleen. This can occur in disease states in adults when bone marrow becomes destroyed or fibrosed and is called extramedullary haematopoiesis.

All blood cells are derived from pluripotent uncommitted stem cells that differentiate into one or other type of committed stem cell (progenitor cell). These in turn differentiate into various types of blood cell (Figure 1).

Only 25% of cells in active marrow belong to the erythrocyte producing series compared with 75% that mature into leucocytes even though there are 500 times as many erythrocytes in the circulation as leucocytes. This is because the lifespan of the leucocyte is short (hours–21 days) compared to the erythrocyte life span (approximately 120 days).

The development of erythrocytes, termed erythropoiesis, from their dedicated stem cell (pronormoblast) within the bone marrow takes 5–7 days. As differentiation proceeds, the cells shrink, haemoglobin is synthesized and in the later stages the nucleus breaks up and disappears. After the final division the cells evolve through the reticulocyte stage, so-called as a reticulum (mesh-like system of ribosomal RNA) can be seen on staining. This then disappears as the cells become mature biconcave discs. Normally, approximately 1–2% of circulating

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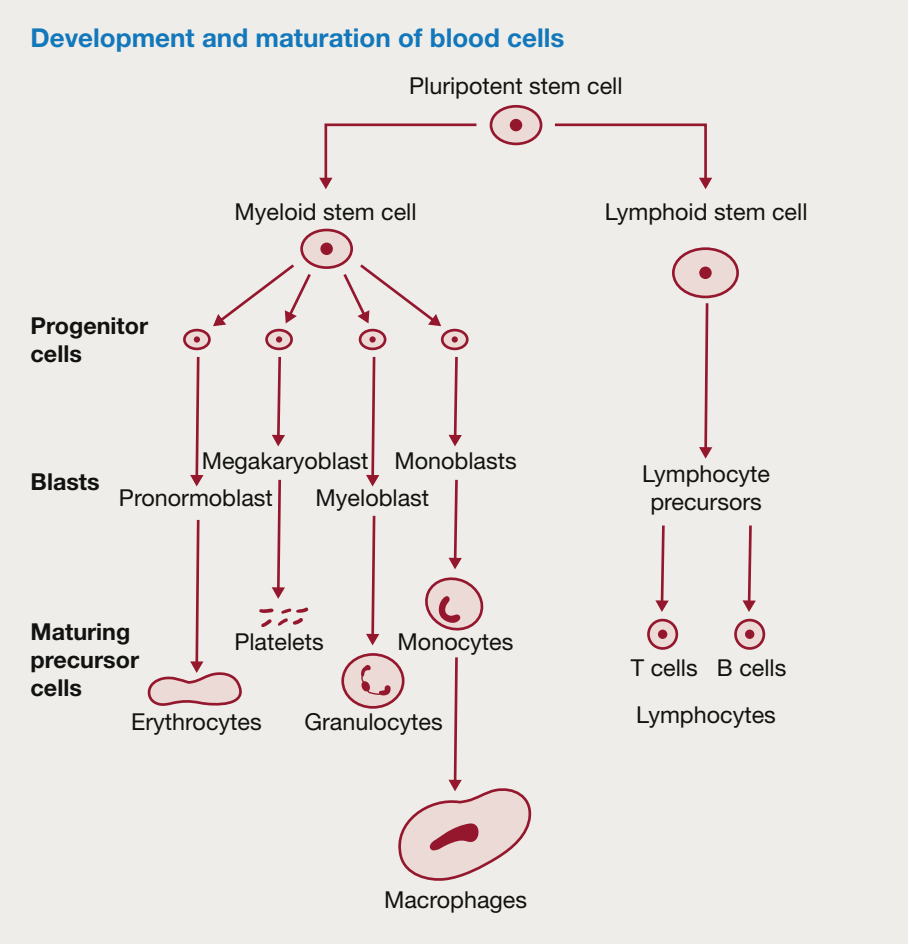

Figure 1

erythrocytes are at the reticulocyte stage. This percentage does increase in certain circumstances such as major blood loss or chronic anaemia when increased erythropoiesis is triggered.

Erythropoiesis is subject to feedback control. It is inhibited by a rise in circulating erythrocytes to a supranormal level and stimulated by anaemia and hypoxia. This feedback control of red cell production is mediated by erythropoietin, a circulating glycoprotein hormone secreted from the juxtaglomerular apparatus of the nephron in response to hypoxia or anaemia.

Over time erythrocytes become damaged or lose shape. These abnormally shaped cells are then sequestered in the spleen and to a lesser extent the liver. At sequestration the haem group is split from haemoglobin and converted to biliverdin and then bilirubin which is excreted in bile while the iron is conserved and recycled via the iron transport protein transferrin or stored in ferritin.

Haemoglobin

Haemoglobin (Hb) is a metalloprotein within the erythrocyte responsible for over 99% of oxygen carriage from the lungs to the tissues and accounting for 33% of red cell mass. It comprises of four subunits each containing a polypeptide globin chain and an iron-containing porphyrin called haem. The haem is synthesized from succinic acid and glycine and contains one atom of iron in the reduced, ferrous state (Fe^{2+}). One molecule of Hb has four atoms of iron and binds four molecules of oxygen. There are two pairs of polypeptide globin chains in each Hb molecule. Normal adult haemoglobin (HbA) contains two α and two β chains. Another normal variant (HbA_2) accounts for up to 2.5% of Hb and contains two α and two δ chains. Fetal Hb (HbF) contains two α and two γ chains. The difference in structure of the γ chains gives HbF a greater affinity for oxygen thereby allowing the offload of oxygen from the maternal to the fetal circulation.

Oxygen delivery to the tissues and the oxygen dissociation curve

When oxygen (O_2) binds to haemoglobin it forms oxyhaemoglobin. This is a reversible reaction ($O_2 + Hb \leftrightarrow HbO_2$). The quaternary structure of Hb determines its affinity for oxygen. When adult haemoglobin (HbA) takes up O_2 the two β chains move closer together, when O_2 is given up they move further apart. Movement of the chains causes a change in the position of the haem groups which assume a relaxed (R) state that favours O_2 binding or a tense (T) state that reduces O_2 binding. When Hb binds with oxygen the R state is favoured and additional uptake is facilitated. Combination of the first haem group in the Hb molecule with oxygen increases the affinity of the second haem group for oxygen which consequently increases the affinity of the third haem group for oxygen and so on, meaning that the affinity of the Hb for the fourth oxygen molecule is many times that of

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the first. This property known as haem–haem interaction results in a sigmoidal curve when saturation is plotted against the partial pressure of oxygen (PO_2) in an oxygen dissociation curve (Figure 2). This high affinity of Hb for oxygen means that total saturation occurs at an alveolar PO_2 of 13 kPa. This haem–haem interaction also has an advantage at the tissues as the reverse is also true where a smaller fall in PO_2 is required at the tissues for a given amount of oxygen to be released, thereby encouraging O_2 offload. In contrast the dissociation curve for myoglobin is hyperbolic, meaning that while myoglobin has a high affinity for oxygen it does not give up oxygen readily, this is an advantage in its role as an oxygen storage protein in muscle (Figure 2).

The affinity of haemoglobin for oxygen is affected by:

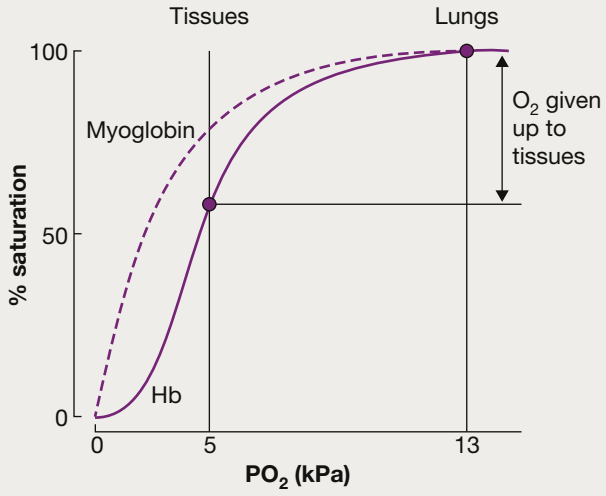
- pH
- temperature
- 2,3 diphosphoglycerate (2,3 DPG) concentration.

An increase in temperature or decrease in pH will shift the oxygen dissociation curve to the right, meaning that a higher PO_2 is required for Hb to bind to a given amount of oxygen (Figure 3).

The decrease in Hb affinity for oxygen when the pH falls is called the Bohr effect and is closely related to the fact that deoxyhaemoglobin binds hydrogen ions more actively that oxyhaemoglobin. The pH of the blood falls as the carbon dioxide (CO_2) content increases in the tissues so that when the partial pressure of carbon dioxide (PCO_2) rises the oxygen dissociation curve shifts to the right meaning that the haemoglobin has a lower affinity for oxygen, again encouraging offload of oxygen at the tissues.

2,3 DPG is plentiful in erythrocytes, it is a by-product of red cell glycolysis and a highly charged anion that binds to the β chains of deoxyhaemoglobin. An increase in 2,3 DPG shifts the oxygen dissociation curve to the right causing more oxygen to be liberated in the tissues (Figure 3). Situations that lead to an increase in 2,3 DPG concentration are release of thyroid hormones, growth hormones and androgens, exercise, ascent to high altitude and chronic hypoxia.

Traditionally, stored blood in blood bank has decreasing 2,3 DPG levels over time, meaning that this blood may be less effective at releasing oxygen to the tissues as the oxygen dissociation curve shifts to the left. Effects such as these have led to the selective use of more freshly donated blood by clinicians in the most vulnerable patients and/or those receiving chronic transfusions (e.g. premature newborn and sickle cell disease, respectively).



Hb, haemoglobin; PO_2, partial pressure of oxygen.

Figure 2

Carbon dioxide carriage and buffering

The erythrocyte has an important role in the transport of carbon dioxide (CO_2) from the tissues to the lungs. Although CO_2 is 20 times more soluble that O_2, only up to 7% of CO_2 is transported dissolved in the plasma. The vast majority of CO_2 undergoes a chemical reaction within the erythrocyte either via a hydration reaction catalysed by carbonic anhydrase and converting CO_2 to bicarbonate ions (70%) or by combining directly to haemoglobin to form a carbaminohaemoglobin compound.

Figure 4 diagrammatically represents the reversible hydration reaction occurring in the erythrocyte as carbon dioxide (CO_2) combines with water (H_2O) to form H_2CO_3. This reaction can take place in the plasma but the plentiful presence of the enzyme carbonic anhydrase within the erythrocyte accelerates the rate of reaction 5000-fold. H_2CO_3 is a weak acid and quickly dissociates to hydrogen ions (H^+) and bicarbonate ($HCO3^-$). The hydrogen ions are predominantly buffered by haemoglobin while the bicarbonate ions enter the plasma in exchange for chloride ions. This exchange is called the chloride shift. The chloride content of erythrocytes in venous blood is therefore higher than in arterial blood. The shift of chloride into the erythrocytes leads to an increase in osmolality causing the erythrocytes to swell. In the lungs the chloride moves out of the red cells and they shrink back down.

Deoxygenated haemoglobin binds more hydrogen ions than oxygenated haemoglobin and forms carbamino compounds more readily meaning that venous blood can carry more CO_2 than arterial blood. This increased capacity of deoxygenated blood for CO_2 transport is called the Haldane Effect and is another factor that encourages CO_2 uptake in the tissues and transport in the venous circulation to the lungs.

White blood cells

White blood cells (leucocytes) are far less numerous in the blood than erythrocytes, with a cell count of $4–11 \times 10^9$/l under normal conditions, accounting for less than 1% of total blood volume. There are several different types of leucocyte, varying in size, structure and function. They contain nuclei and other organelles but do not contain haemoglobin. Collectively they form the body's main defence against disease; protecting against damage from pathogens and removing damaged cells, toxins and waste products. They can be divided by several different characteristics but a common differentiation is between granulocytes and agranulocytes.

Granulocytes are neutrophils, eosinophils and basophils. They are all roughly spherical in shape and have lobar nuclei. They contain cytoplasmic granules that are easily stained and

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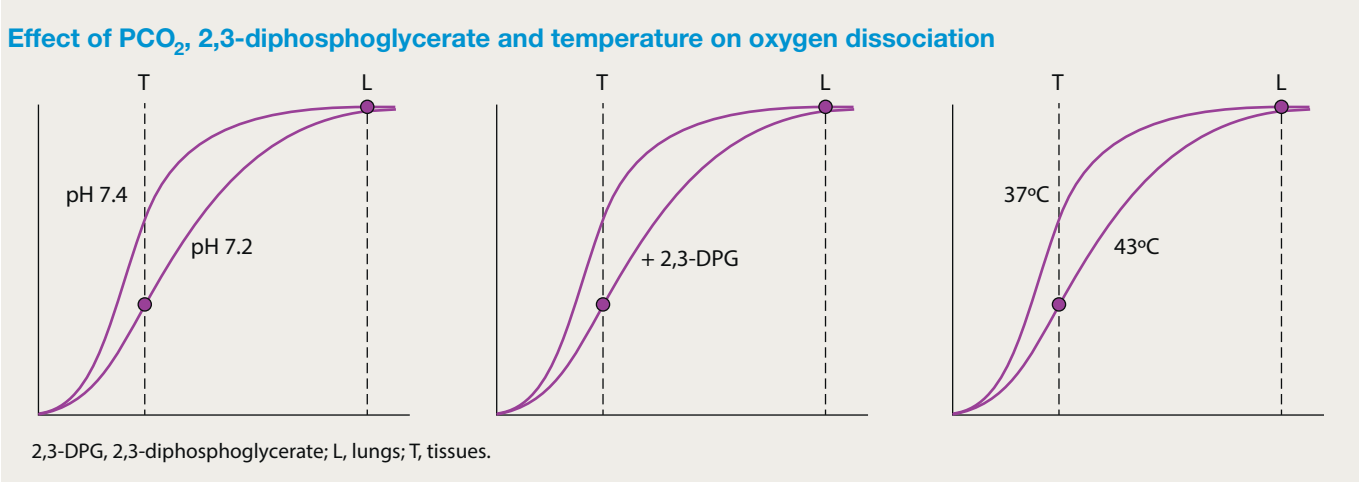

Figure 3

seen on microscopy. They are non-specific as they can be activated by a number of different stimuli.

Agranulocytes consist of lymphocytes and monocytes (precursors of macrophages). While they do still contain secretory vesicles these are hard to see under light microscopy, hence the term agranulocytes. They are quite distinct from each other functionally but are structurally similar.

Leucocytes have several distinguishing characteristics:

- *Migration*: Leucocytes migrate out of the blood stream and spend most of their lifespan outside of the circulation in the body's tissues performing their defensive function. They are able to pass between the endothelial cells of the capillary blood vessels, this is known as diapedesis. The circulation is merely their transport to the areas of the body where they are needed.
- *Movement:* They are capable of amoeboid movement. They form extensions and the flow of cytoplasm within these allows them to move along the tissue space.
- *Positive chemotaxis:* Chemical molecules released by damaged tissues or other leucocytes attract white blood cells to areas in which they are needed, this is known as positive chemotaxis. This leads to leucocytes gathering in large numbers to destroy foreign pathogens and dead cells.

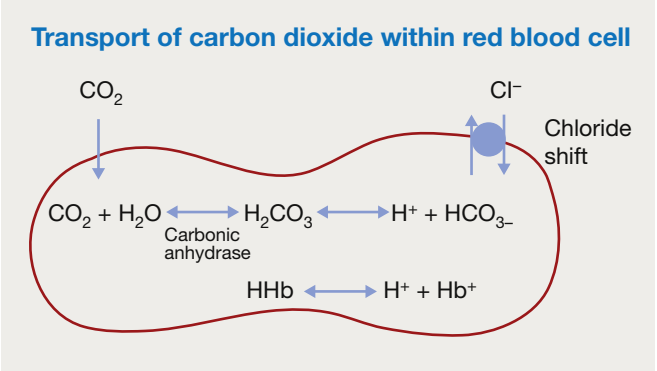

Figure 4

- *Phagocytosis:* Neutrophils, eosinophils and monocytes are phagocytes, which means they are capable of engulfing and absorbing other small cells and particles.

Like erythrocytes, the leucocytes are initially produced in the bone marrow by myeloid stem cells. These myeloid stem cells divide to form different progenitor cells (Figure 1). Monocytes and neutrophils share a common progenitor whereas eosinophils and basophils have two separate progenitor cells. Monocytes complete differentiation into macrophages in the peripheral tissues. Although most leucocytes develop in the bone marrow, lymphocytes are an exception. They arise from a common progenitor in the bone marrow but migrate to different sites in the lymphoid tissues (thymus, spleen and lymph nodes) where much of their development and reproduction takes place.

Leucocyte formation is stimulated by many factors most of which are released by the mature leucocyte in order to recruit more leucocytes to a site of infection or injury. As a result, leucocyte numbers increase dramatically during an infection.

Neutrophils are the most common form of leucocyte, accounting for 50–70% of circulating white blood cells. They are approximately twice as large as erythrocytes and are also known as polymorphonuclear leucocytes, due to the lobular structure of their dense nuclei. They are phagocytic cells which form the body's first line of defence against bacterial infection. They are highly mobile and in bacterial infection they migrate through the capillary endothelium, attracted to the site of an inflammatory response by chemotactic substances from the damaged tissues. They recognize bacteria that have been labelled with antibodies or complement proteins (a group of 11 blood-borne proteins that bind to bacteria in a cascade, attracting phagocytes and forming pores in the bacterial membrane to promote lysis). Neutrophils contain granules, some of which contain hydrolytic enzymes. These are known as lysosomes. Other granules contain proteins called defensins which, when released, form large holes in the cell membrane of bacteria, fungi and some viruses aiding the destruction of the foreign body. During phagocytosis oxygen is metabolized to form hydrogen peroxide (H_2O_2) and superoxide anions (O_2^-) which can also kill pathogens. Neutrophils release prostaglandins which increase blood flow and vascular permeability, allowing the passage of exudate into the damaged area

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causing inflammation. Leukotrienes are also secreted and attract other phagocytes to the site of infection. Neutrophils have a short life span of around 10 hours, but when they are actively engulfing bacteria this can be shortened to as little as 30 minutes. The death of neutrophils in large numbers forms purulent necrosis (pus).

Eosinophils account for 2–4% of circulating leucocytes. They are similar in size to neutrophils and have a bi-lobed nucleus. Eosinophils will engulf antibody-tagged bacteria and cell debris but their main role is defence against parasites (e.g. tapeworms, flukes and pin worms). These parasites are too large to be ingested but eosinophils have granules which contain unique digestive enzymes. Parasites often enter the body through the skin or via ingestion and tend to reside in the respiratory or gastrointestinal mucosa. Eosinophils are found in large numbers in these areas and when they encounter a parasite they release digestive enzymes to attack the parasite. Eosinophils also have a complicated role in allergic reactions during which they increase in number. By phagocytosing immune complexes and inactivating some inflammatory chemicals they can lessen the severity of an allergic reaction. Their other role is modulation of inflammation, restricting the inflammatory actions of neutrophils and mast cells to the site of injury or infection.

Basophils represent only 1% of leucocytes and are slightly smaller than neutrophils. They migrate to sites of injury and release histamine which causes vasodilation and increased blood flow to the area and attracts other leucocytes. They also release heparin which prevents blood clotting and ensures good blood flow to the area. They are microscopically similar to mast cells and both bind to IgE.

Monocytes are larger than the other white blood cells and account for 2–8% of leucocytes. They may also be distinguished by their oval or kidney-shaped nucleus. They spend only a short time in the circulation (24 hours) before entering the tissue where they differentiate to become macrophages. Macrophages are highly mobile and actively phagocytic. They can engulf large objects and so are important in defence against viruses, parasites and chronic infections, such as tuberculosis. During phagocytosis they release signals that attract neutrophils and monocytes, as well as other macrophages. They also attract fibroblasts, which in turn produce scar tissue in order to isolate the injured area.

Lymphocytes account for 20–30% of circulating white blood cells, but actually spend very little time in the circulation. Lymphocytes are responsible for the specific defence response to infection known as immunity. They may be divided into three types: B cells, T cells and natural killer (NK) cells.

B cells mature in the bone marrow (hence the name B cells) then pass between the spleen/lymph nodes and the circulation. Their role is to produce antibodies once they have encountered a specific antigen. (An antigen is a foreign substance which induces an immune response. Antibodies are proteins produced in response to a specific antigen.) They then bind to the antigen and prime the foreign cell for phagocytosis. When an immature B cell encounters an antigen which it recognizes it ingests the cell. Major histocompatibility complex (MHC) II molecules which are present on the surface of the B cell then present fragments of the ingested antigen. This cell must then combine with its matching type 2 T-helper cell to complete maturation and become an antibody-producing B cell. B cells do not have to travel to the site of invasion as the antibodies can travel throughout the circulation.

T lymphocytes mature in the thymus (hence the name T cells) and also travel between the spleen/lymph nodes and circulation. T cells are responsible for cell-mediated immunity; this is the main defence against viral and fungal infections, as well as playing a role in delayed hypersensitivity reactions and transplant rejection. Macrophages and dendritic cells present antigens to the T cells which activates the production of cytokines. In turn this results in the differentiation of different sub-classes of T cells, these are divided by the presence of cell surface protein markers – CD4 and CD8.

- CD8 cells are the cytotoxic T cells (TC cells). They coordinate cell-mediated immunity by migrating to sites of foreign cell invasion and attacking cells in conjunction with other lymphocytes.
- CD4 helper T cells (TH cells) differentiate into two types. TH-1 activate macrophages to destroy intracellular organisms. TH-2 cells activate B cells, as described above, to produce antibodies.
- Suppressor T cells (TS cells) inhibit T cell and B cell activation, moderating the immune response.

The third class of lymphocyte is the NK cell, which is responsible for immunological surveillance of normal tissues. NK cells are non-antigen specific so they are activated by a different mechanism to the cytotoxic cells but this is not known. They will recognize and attack any foreign antigen on any membrane therefore they act quickly and non-specifically. Once an abnormal cell is detected, the NK cell attaches itself to the target cell. Vesicles then release a protein called perforin which binds to the cell membrane of the abnormal cell, creating pores. This process destroys the cell membrane, allowing ions and protein to diffuse out of the cell. This quickly causes cellular disintegration. This mechanism allows for the recognition and destruction of cancer cells, which express tumour specific antigens, or cells infected by viruses. Unfortunately, NK cells also target transplanted cells and thus play a role in the rejection of allogenic bone marrow cells and solid organ transplants. ◆

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