

Structure and function of red and white blood cells

Barbara J Bain

Abstract

Red cells have a major function in transport of oxygen and minor functions in regulation of local blood flow and transport of carbon dioxide. Neutrophils and monocytes are phagocytic cells that are part of the innate and also the adaptive immune response. Eosinophils have their major function in protecting against multicellular parasites, and basophils participate in this process. B cells are part of the adaptive immune response, specifically differentiating to plasma cells, which are responsible for humoral immunity. Some T cell subsets and natural killer (NK) cells mediate cellular immunity, both innate and adaptive, while other T cell subsets suppress the activity of B cells, helper T cells and cytotoxic T cells. NK cells and cytotoxic T cells are important in defence against tumours.

Keywords B cell; basophil; cytotoxic T cell; eosinophil; eryptosis; erythrocyte; haemoglobin; helper T cell; leucocyte; lymphocyte; monocyte; natural killer cell; neutrophil; oxygen transport; red cell; red cell senescence; reticulocyte; suppressor T cell; T cell; white cell

Introduction

The red cells (erythrocytes) and white cells (leucocytes) are normally produced in the bone marrow, being ultimately derived from a pluripotent haemopoietic stem cell. White cells comprise granulocytes (neutrophils, eosinophils, basophils), monocytes and lymphocytes. Note that the term 'granulocyte' should not be used as a synonym for neutrophil; it has a broader meaning.

Red cells

The human red cell can be regarded as a miracle of evolution. Once past the reticulocyte stage, it has lost not only its nucleus, but also organelles such as mitochondria, Golgi apparatus and endoplasmic reticulum with its ribosomes, and has assumed the form of a hollowed-out disc. This disciform shape provides a large surface for the exchange of oxygen. The lack of organelles means that the red cell is flexible and can easily deform to pass through capillaries and splenic sinusoids.

Haemoglobin is a metalloprotein composed of four α - or α -like and two β - or β -like globin chains, each globin chain enclosing a haem moiety. The major function of red cells is the uptake of oxygen from the lungs and its delivery to the tissues, by oxygenation of the ferrous (Fe^{++}) ions of haem. Around 98% of oxygen transport is by red cells, only 2% being transported in the

Key points

- Erythrocytes have a major function in oxygen transport, with more minor roles in transport of carbon dioxide and regulation of vasodilation
- Neutrophils and monocytes are phagocytic cells that contribute to both innate and adaptive immune responses
- Monocytes differentiate into macrophages, which function as phagocytes, antigen-presenting cells and immune modulators, and in iron storage
- Eosinophils and basophils have a role in protecting against parasitic infections
- Lymphocytes interact with neutrophils, monocytes, macrophages and dendritic cells, and have a major role in innate and adaptive immune responses

plasma. The red cell has a diameter greater than that of a capillary; the need to deform and squeeze through the capillary is likely to improve transfer of oxygen from the erythrocyte to the tissues.

The red cell is also capable of transporting carbon dioxide from the periphery to the lungs, by binding carbon dioxide, as carbamate, to the N-terminal end of the α -globin chain, with its subsequent release as carbon dioxide in the lungs. However, the red cell is only responsible for transporting about 15% of the carbon dioxide, the rest being transported in the plasma. Deoxyhaemoglobin also functions to generate nitric oxide from nitrite, and can thus contribute to vasodilation in the peripheral tissues. The confining of haemoglobin within the red cell means that there is protection against the ability of oxyhaemoglobin to inactivate nitric oxide, which occurs when there is intravascular haemolysis, leading to vasoconstriction and a thrombotic tendency.

The constituent parts of the haemoglobin molecule are synthesized and assembled in erythroblasts in the bone marrow. This requires the presence of ribosomes, on which globin chains are assembled, and mitochondria, which are required for some stages of haem synthesis. The reticulocyte retains mitochondria and ribosomes. This means that haemoglobin synthesis can continue for the 1–2 days the reticulocyte spends in the circulation, and up to 10% of such synthesis occurs in these cells. The pairing of two dissimilar globin chains and the cooperativity between them are essential for the sigmoid oxygen dissociation curve, which ensures efficient uptake of oxygen in the lungs and efficient delivery in the tissues (Figure 1). The oxygen affinity of normally structured haemoglobin means that such uptake and delivery of oxygen is achieved at a red cell count/haemoglobin concentration/haematocrit that does not lead to hyperviscosity.

Other requirements must be met for the red cell to fulfil its major function – transporting oxygen. The following are

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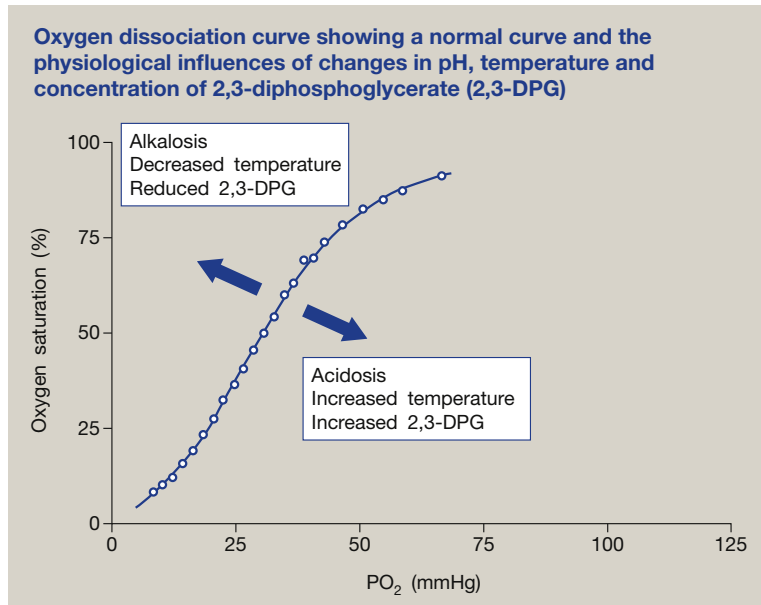


Figure 1

essential for normal function: a permeable membrane; maintenance of the disciform shape and cell flexibility; the ability to convert methaemoglobin (which is spontaneously produced and cannot transport oxygen) to haemoglobin; production of energy in the form of adenosine triphosphate and generation of a reduction potential in the form of nicotinamide adenine dinucleotide (NADH) by means of the Embden–Meyerhof pathway; generation of further reduction potential in the form of NADH phosphate (NADPH) by means of the pentose shunt; and the ability to produce 2,3-diphosphoglycerate (2,3-DPG), which interacts with the haemoglobin tetramer to reduce oxygen affinity and improve oxygen delivery to the tissues. An increased concentration of 2,3-DPG can compensate for anaemia. NADH and NADPH protect the erythrocyte from endogenous and exogenous oxidants. Relevant metabolic pathways are summarized in Figure 2.

The structure of the red cell reflects its function: a cell membrane encloses cytoplasm that has haemoglobin as the major component, with carbonic anhydrase the second most abundant protein. The membrane is composed of a lipid bilayer through which pass various proteins with diverse functions including the transport of anions, water and glucose and the binding of the lipid bilayer at various points to the underlying cytoskeleton, thus maintaining the cell shape (Figure 3). The cell membrane has other functions at the end of the erythrocyte's lifespan of about 120 days. Red cell senescence is the result of a conformational change in a membrane protein, band 3, leading to the appearance of a senescence-specific antigen recognized by autologous immunoglobulin (Ig) G, marking the cells for removal by macrophages.¹ In addition, aged red cells are also more

susceptible to oxidant stress and therefore to eryptosis. In this process, there is externalization of membrane phosphatidylserine leading to binding to CD36, the phosphatidylserine receptor on macrophages, with resultant phagocytosis.¹

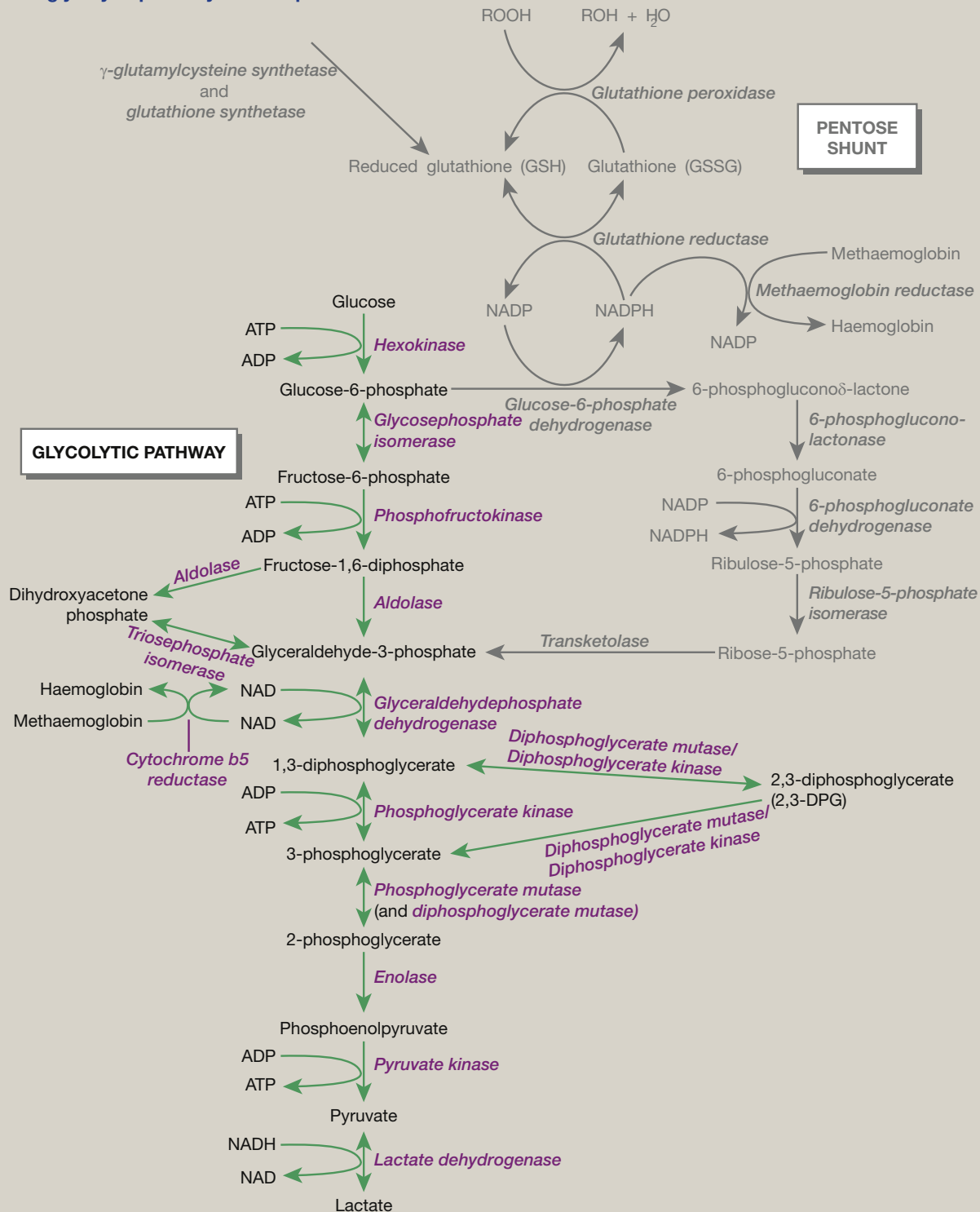
Neutrophils

Polymorphonuclear neutrophils are produced in the bone marrow and circulate in the blood before migrating to the tissues, where their main functions are fulfilled. Their lifespan in the circulation is about 7–10 hours and in tissues is 1–2 days. Most neutrophils have a nucleus divided into two to five lobes separated from each other by a thin filament. A minority, referred to as band forms, have a non-lobulated nucleus in the shape of a curved band; with maturation, the nucleus of the band forms develops lobes.

The neutrophil cytoplasm contains some ribosomes, small numbers of mitochondria, glycogen and granules of various types.² Only the primary or azurophilic granules are visible by light microscopy. On May–Grünwald–Giemsa (MGG)-stained blood films, they are lilac. They contain myeloperoxidase, defensins, lysozyme, neutrophil elastase and cathepsin G. The secondary, specific or neutrophilic granules are visible by electron microscopy, and on MGG-stained films are responsible for the pink tinge of the cytoplasm. They contain lactoferrin, transcobalamin, collagenase, gelatinase, lysozyme and cathelicidin. Tertiary granules, also below the level of resolution of the light microscope, contain gelatinase and lysozyme. Neutrophil alkaline phosphatase is contained within secretory vesicles.

Neutrophils are part of the innate immune system. Their functions include: margination; adhesion to the endothelium; transcellular and paracellular migration through the endothelium

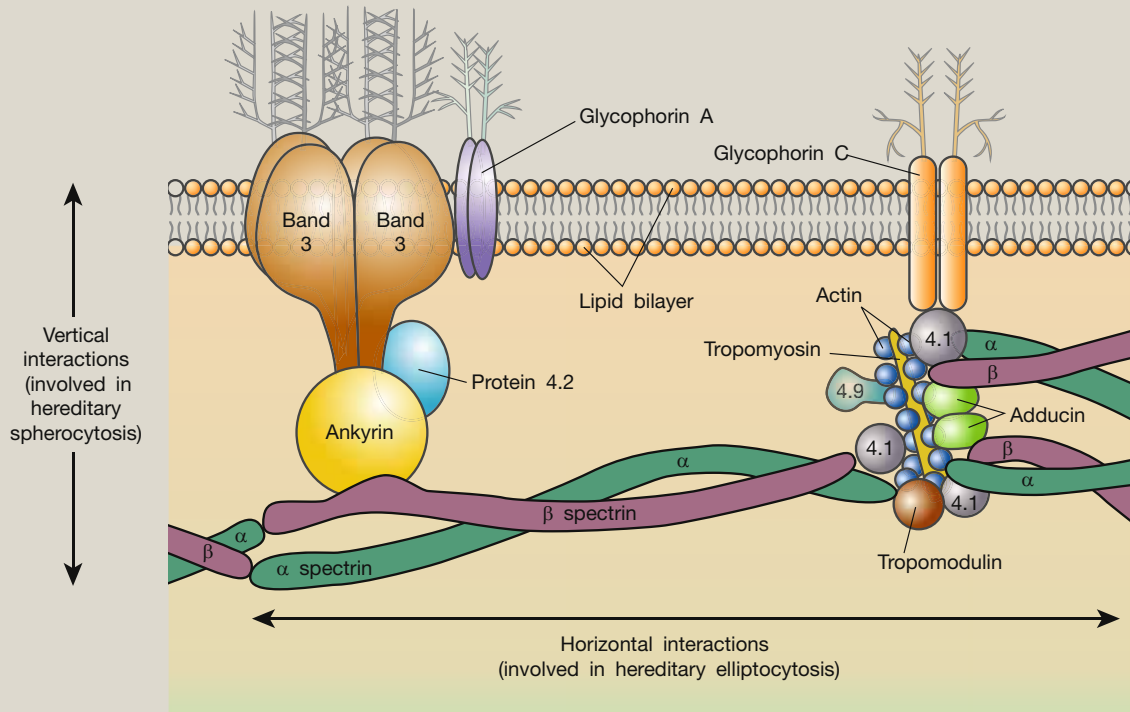
The glycolytic pathway and the pentose shunt



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Diagram of the red cell membrane



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Figure 3

(diapedesis); movement through the tissues in response to chemotactic stimuli (chemotaxis); phagocytosis, killing and digestion of microorganisms; and phagocytosis and digestion of dead cells and cellular debris (Figure 4).³

Margination and rolling along the endothelium is achieved by selectins on the neutrophil surface membrane. Adhesion requires adhesion molecules, which are upregulated in infection and inflammation. Chemotaxis occurs as a result of the presence of membrane receptors that can detect complement 5a and various cytokines, such as interleukin (IL)-8 and interferon- γ , allowing the neutrophil to migrate against a concentration gradient. The process of phagocytosis is enhanced when microorganisms are opsonized by complement or Ig.

Phagocytosis is followed by fusion of granules to the phagocytic vacuole (phagosome), with granule contents, including proteolytic enzymes, being emptied into the phagosome. A respiratory burst then leads to generation of hypochlorous acid plus hydrogen peroxide and other activated oxygen species within the phagosome. This, plus the action of proteolytic enzymes, leads to killing and digestion of microorganisms and digestion of other phagosome contents. Killing of microorganisms is further enhanced by generation of neutrophil extracellular traps.⁴ These comprise a lattice of extracellular chromatin fibres (DNA,

histones) together with proteolytic granule proteins. Their formation is triggered by reactive oxygen species. They mediate extracellular killing of microorganisms (bacteria, fungi) and can also create a physical barrier around an area of infection.

Eosinophils

Polymorphonuclear eosinophils are slightly larger than neutrophils. The nucleus is usually bilobed. Eosinophils have acidophilic granules, which are larger than those of neutrophils. On an MGG-stained film, they are orange because of their affinity for the eosin component of the stain. Occasionally, particularly in reactive eosinophilia, there are some purple proeosinophilic granules. In addition to granules, the weakly basophilic cytoplasm contains abundant glycogen particles and more numerous and larger mitochondria than are found in neutrophils; there is also some rough endoplasmic reticulum.² The granules have a crystalline core composed of eosinophil major basic protein surrounded by a matrix containing eosinophil cationic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, plasminogen, ribonucleases, deoxyribonuclease and lipase. The eosinophil lifespan is about 1 day in the circulation and 8–12 days in the tissues.

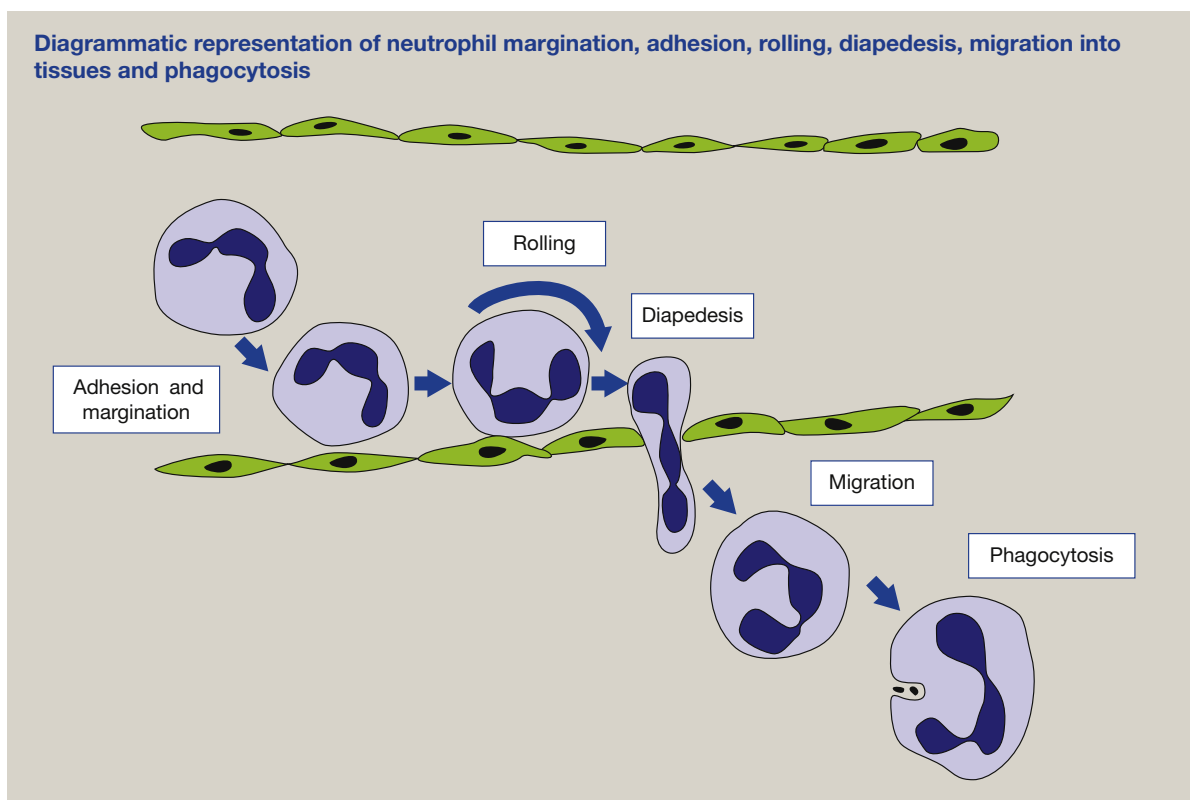


Figure 4

Eosinophils synthesize and secrete growth factors, cytokines and chemokines; they have a role in the regulation of innate and adaptive immune responses and in tissue remodelling and repair. They trigger release of histamine by basophils and mast cells, and are important in the control of infection by multicellular parasites. They are attracted to the sites of parasitic infection by chemokines such as eotaxin 1 and 2, and at such sites are activated by cytokines produced by helper T cells. They attack parasites by degranulation and peroxidase-mediated generation of reactive oxygen species. Eosinophil neurotoxin and ribonuclease have antiviral properties.

In addition to their useful functions, eosinophils are implicated in maladaptive allergic conditions. They can also cause collateral damage to normal tissues as a result of the eosinophil response to parasitic infection.

Basophils

Polymorphonuclear basophils are granulocytes which, on MGG-stained films, have large dark purple granules that almost obscure the nucleus. The nucleus is usually bilobed. Basophils survive many days in the circulation. In addition to the granules, the cytoplasm contains scattered glycogen particles, membrane whorls, Golgi apparatus, a few mitochondria and a small amount of rough endoplasmic reticulum.² Basophils have some

phagocytic activity and degranulate when IgE binds to a specific membrane receptor. They have a role in protection against helminth infections but are also involved in allergy, anaphylaxis and chronic inflammation; they secrete histamine, serotonin, heparin, proteolytic enzymes, IL-4 and IL-13.

Monocytes

Monocytes are the largest peripheral blood cells. On MGG-stained films, they have an irregular, usually lobulated, nucleus and opaque greyish-blue cytoplasm containing fine azurophilic granules and often vacuoles. They are phagocytic cells and are part of the innate immune system. However, their functions are broader than those of neutrophils. They retain proliferative capacity and, following migration to tissues, differentiate into macrophages and other specialized cells of the reticuloendothelial system, and into dendritic cells and osteoclasts. Some cells (e.g. Kupffer cells of the liver) are fixed, while other remain mobile.

In addition to phagocytosis and killing of microorganisms (including mycobacteria, *Listeria* and fungi), monocytes are antigen-presenting cells and thus involved in lymphocyte selection and activation. They are immune modulators, secreting IL-1, IL-6, IL-12, tumour necrosis factor- α , interferon- α and interferon- β when stimulated, thus enhancing the

Subsets and function of T cells and natural killer (NK) cells

Type of lymphocyte	Subsets	Function
CD4-positive (approximates to helper subset)	Natural regulatory T cell NK-like T cell	Regulation of immune responses Anti-tumour immunity following activation by antigens
	Type 1 helper T cell	Immunity to intracellular pathogens (activation of macrophages, mediation of cytotoxicity, promotion of cellular immune responses), induce delayed hypersensitivity
	Type 2 helper T cell	Immunity to many extracellular pathogens including helminths (promote B cell proliferation and antibody secretion, induce IgE secretion, recruit eosinophils to sites of inflammation)
	Type 17 helper T cell	Immunity to extracellular bacteria and fungi (recruit and activate neutrophils, increase monocyte production); can mediate acute graft-versus-host disease
	Induced regulatory T cell	Immune tolerance (self-tolerance, tolerance of allografts), lymphocyte homeostasis, regulation of immune responses
CD8-positive (includes cytotoxic and suppressor subsets)	Cytotoxic T cells	Antigen recognition in a human leucocyte antigen class I context with resultant cytotoxicity; important in defence against viral infections and in allograft rejection
	Suppressor T cells	Suppress the activities of B cells, cytotoxic T cells and helper T cells
NK cells	NK cells (cytologically large granular lymphocytes)	Direct killing of virus-infected cells or tumour cells by cytotoxic granule contents Antibody-dependent cellular cytotoxicity Production of immunoregulatory cytokines

Table 1

inflammatory response. On ultrastructural examination, the cytoplasm contains heterogeneous granules, glycogen particles, mitochondria, an active Golgi apparatus and short lengths of endoplasmic reticulum.² Their intravascular lifespan is 1–3 days, while the cells into which they differentiate are long-lived.

Macrophage functions include the removal of unicellular parasites from erythrocytes, removal of Howell–Jolly bodies and other red cell inclusions, removal from the circulation of senescent red cells, phagocytosis of other senescent or dead cells, storage of iron as ferritin and haemosiderin, and supply of iron to developing erythroblasts. Macrophage activity has some adverse effects, specifically in the pathogenesis of anaemia of chronic disease.

Lymphocytes

Lymphocytes are the smallest leucocytes, approximately round with a fairly round nucleus. Most have scanty cytoplasm, but some have more plentiful cytoplasm with or without granules. They can thus be divided cytologically into small lymphocytes, large lymphocytes and large granular lymphocytes. On ultrastructural examination, their features are very variable: there is heavy chromatin condensation, the cytoplasm may or may not

contain acid phosphatase-positive granules, and may contain mitochondria; there are abundant free ribosomes, variable amounts of rough endoplasmic reticulum and usually a small and inactive Golgi apparatus.²

Functionally, lymphocytes are divided into B cells, T cells and natural killer (NK) cells. B cells migrate to tissues and differentiate into memory B cells and Ig-secreting plasma cells. T and NK cells are involved in cellular immunity, both innate and adaptive.⁵ Their functions are summarized in Table 1. Lymphocytes recirculate between the blood and tissues. Their lifespan is very variable. ♦

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