Structure and function of red and white blood cells

Ted Gordon-Smith

Abstract

Red blood cells (RBCs) carry oxygen bound reversibly to the ferrous Fe^{2+} atoms of the four haem groups of the haemoglobin (Hb) tetramer. In order to transport the Hb around the body in a functional state, the RBC requires a flexible membrane and contents to pass passively through the capillary bed and a source of energy to maintain the internal milieu. Adenosine triphosphate is provided by anaerobic glycolysis. Reducing power is provided as NADH and NADPH, via the pentose phosphate pathway. Genetic abnormalities that affect the membrane deformability lead to shape changes and haemolysis; defects in the glycolytic pathway cause non-spherocytic haemolytic anaemia and failure of reducing power to intravascular haemolysis in response to oxidative stress. RBCs may also control local blood flow through vasodilatation produced by the nitrite—nitic oxide pathway. White blood cells provide the basis for the innate immune system as well as interacting with specific immune processes. They need to pass from the circulation, through the vessel wall into the extravascular tissues in order to carry out these functions. Inherited defects of the migratory process also lead to susceptibility to infection. The phagocytic neutrophils and macrophages have specialized systems for rapid recognition of pathogens, and systems for killing and antigen presentation.

Keywords allosteric; cell adhesion; erythrocytes; glycolysis; granulocytes; migration; monocytes; oxygen carriage; phagocytosis; red blood cells

Values for the numbers of circulating blood cells for normal individuals at different ages are given in Table 1.[1,2] Numbers are maintained within fairly close limits under steady conditions but can be increased rapidly and appropriately in response to stress. The value for each cell type is a reflection of the rates of release into and escape from the circulation. Red cells and platelets have a finite life span within the circulation. Granulocytes and monocytes may be marginated on vessel walls and can leave the circulation rapidly in response to inflammatory signals.

Red blood cells (erythrocytes)

Red blood cells (RBCs) are released into the circulation as *reticulocytes*. Reticulocytes are enucleate cells that contain residual RNA, which gives them a faintly basophilic appearance in blood films and provides the reticulate material in supravitally stained preparations (Figure 1). They are about 20% larger than mature RBCs, contain some mitochondria capable of oxidative respiration and make up 1—2% of the circulating red cells. Values are usually expressed in absolute numbers (Table 1). As reticulocytes pass through the splenic vessels they lose their organelles and RNA is degraded. About half the reticulocyte population resides in the spleen. Although splenectomy increases the number of circulating reticulocytes it does not hinder maturation, nor does it increase the overall RBC count.

The function of RBCs is to carry haemoglobin (Hb) around the body in sufficiently high concentration to allow effective transport of oxygen from the lungs to the tissues, and to facilitate the return of carbon dioxide, produced during oxidative phosphorylation, back to the lungs. To achieve this, RBCs have a suitably large surface area for rapid gas exchange (the biconcave disc shape), a readily deformable structure to pass through the capillary bed, and a source of energy to maintain this structure and provide the internal milieu necessary for functioning haemoglobin.

The red cell membrane

The RBC membrane (Figure 2)[3] is a phospholipid bilayer, stabilized with equimolar amounts of cholesterol. The main phospholipids are phosphatidyl groups linked to ethanolamine, inositol, serine or choline (lecithin) and sphingomyelin. The lipid bilayer provides a stable milieu for the membrane proteins. The proteins determine the shape and flexibility of the RBC. Membrane proteins may be attached to the outer surface of the membrane through integral membrane domains or by the glycophosphatidyl inositol (GPI) anchor. Transmembrane proteins, for example band 3 protein, have both plasma and cytoplasmic domains. External domains include blood groups, binding sites for immune complexes, and the external parts of transmembrane channels and signalling proteins. They are mostly heavily glycosylated, which gives the RBC a strong negative surface charge. Two important complement-inactivating proteins, decay accelerating factor (CD55) and membrane inhibitor of reactive lysis (CD58), are attached via the GPI anchor. Deficiency of these proteins in paroxysmal nocturnal haemoglobinuria is responsible for haemolysis in this condition.

The main proteins of the cytoskeleton are spectrin, actin, protein 4.1 and ankyrin The two chains of spectrin (α and β) wind round each other to form heterodimers, which are linked end to end by actin, protein 4.1 and other proteins to form a network of tetramers on the inner membrane surface (Figure 2). The spectrin is also linked to transmembrane proteins, band 3 and glycophorin C via ankyrin and actin. Together these proteins give the RBC its biconcave disc shape. Mutations in their genes

What's new?

- The possible role of red blood cells and haemoglobin in local blood flow control through the action of nitric oxide
- The importance of specialized phagocytic pathways in neutrophils and macrophages in the innate immune system
- The role of the specialized proteasome in the macrophage family for antigen presentation

Ted Gordon-Smith *MA FRCP FRCP (Ed) FRCPath FAcadMedSci is Emeritus Professor of Haematology and Honorary Consultant Physician at St George's Hospital Medical School, London, UK. Competing interests: none declared.*

Normal values at different ages

	Unit	At birth	Infant	Child	Adult
Haemoglobin	g/dl	15–24	9–13	11–15	M: 13.5–17.5, F: 11.5–15.5
Red blood cells	$\times 10^{12}$/litre	3.7–6.5	3–5	4–5	M: 4.5–6.5, F: 3.9–5.6
Packed cell volume	%	47–75	28–38	32–43	M: 40–52, F: 36–48
Mean corpuscular volume	fl	100–125	84–98	70–90	80–95
Mean corpuscular haemoglobin	pg	31–37	30–36	25–30	27–34
Mean corpuscular haemoglobin concentration	g/dl	32–36	30–35	33–36	20–35
Reticulocytes	$\times 10^9$/litre	120–400	20–60	30–100	30–100
White blood cells	$\times 10^9$/dl	9–30	5–17	6–15	4.0–11.0
Neutrophils	$\times 10^9$/dl	2.7–14.4	1.0–6.0	1.0–8.5	2.0*–7.5
Eosinophils	$\times 10^9$/dl	0.0–0.8	0.09–1.1	0.04–1.04	<0.45
Basophils	$\times 10^9$/dl				<0.1
Monocytes	$\times 10^9$/dl	0.0–1.9	0.4–1.2	0.15–1.28	0.2–0.8
Lymphocytes	$\times 10^9$/dl	2.0–7.25	3.3–11.5	2.3–4.6	1.5–3.5
T (cD8+)	$\times 10^9$/dl			0.8–1.5	0.33–0.67
T(cD4+)	$\times 10^9$/dl			1.0–2.0	0.4–1.8
B cells	$\times 10^9$/dl			0.5–1.5	0.05–0.4
nK cells	$\times 10^9$/dl				0.2–0.4
Platelets	$\times 10^9$/dl	150–450	210–650	170–450	150–450

Figures are derived from several sources,[1,2] which should be consulted for more detailed results for specific ages. They are given here to emphasize the shifts which occur during growth and development. People of African ethnicity may constitutionally have neutrophil counts down to 1.0 $\times$ 10^9/litre.

Table 1

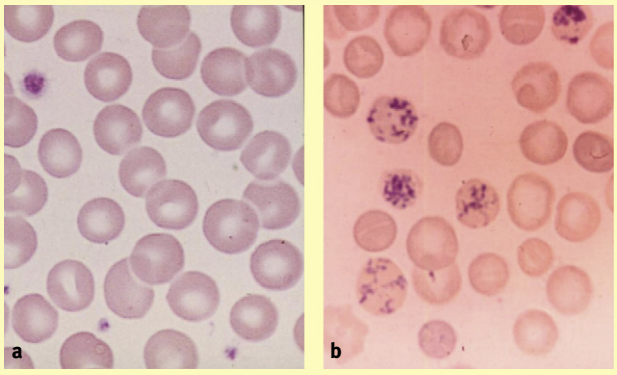
cause haemolytic anaemias associated with abnormalities of shape,[4] the most common being hereditary spherocytosis and elliptocytosis.

Red cell metabolism

The mature RBC derives its energy from anaerobic respiration via the glycolytic (Embden–Meyerhof) pathway, in which one molecule of glucose is converted to two of pyruvate, providing energy as adenosine triphosphate (ATP) and reducing power as NADH. Gene mutations that lead to loss of activity of the enzymes of the pathway lead to shortened RBC survival (non-spherocytic haemolytic anaemias).[5] The most common inherited deficiency of this pathway involves pyruvate kinase (PK). Since reticulocytes can produce energy through oxidative phosphorylation they can bypass the defect. Splenectomy in PK deficiency greatly alleviates the anaemia.

The glycolytic pathway also links to the production of 2,3-diphosphoglycerate (2,3-DPG), a molecule essential for the effective carriage of oxygen by Hb (see below).

The RBC needs reducing power not only to prevent the oxidation of Hb to methaemoglobin, mainly provided by NADH, but also as NADPH to prevent oxidative damage to the red cell membrane. The RBC is subject to attack by reactive oxygen species (ROS) in the circulation and the potentially harmful presence of iron in the Hb. Reduced glutathione (GSH), maintained by the production of NADPH is the main protection from ROS. Inherited mutations of gene on the X chromosome for the enzyme that catalyses the reaction for NADPH, glucose-6-phosphate dehydrogenase, leads to various intravascular haemolytic syndromes, including favism and oxidative drug-induced haemolysis. Free Hb in the circulation is potentially harmful because of the highly reactive haem groups. Free Hb is tightly bound to haptoglobin in a complex that obscures the reactive sites and promotes phagocytosis through specific receptors on macrophages.[6] The pathways of metabolism in the mature RBC are represented in Figure 3, which indicates the main active products.



a Normal red blood cells with area of central pallor the result of the biconcave disc shape. **b** Reticulocytes stained with supravital stain showing reticulate precipitation of RNA.

Figure 1

Haemoglobin and the carriage of oxygen

Hb is a tetramer of two α and two non-α globin chains, each of the chains enclosing one of the four haem groups which carry oxygen in the complete tetramer (Figure 4). The α and α-like

