Blood

Functions of circulatory system

- Hematology (study of blood)

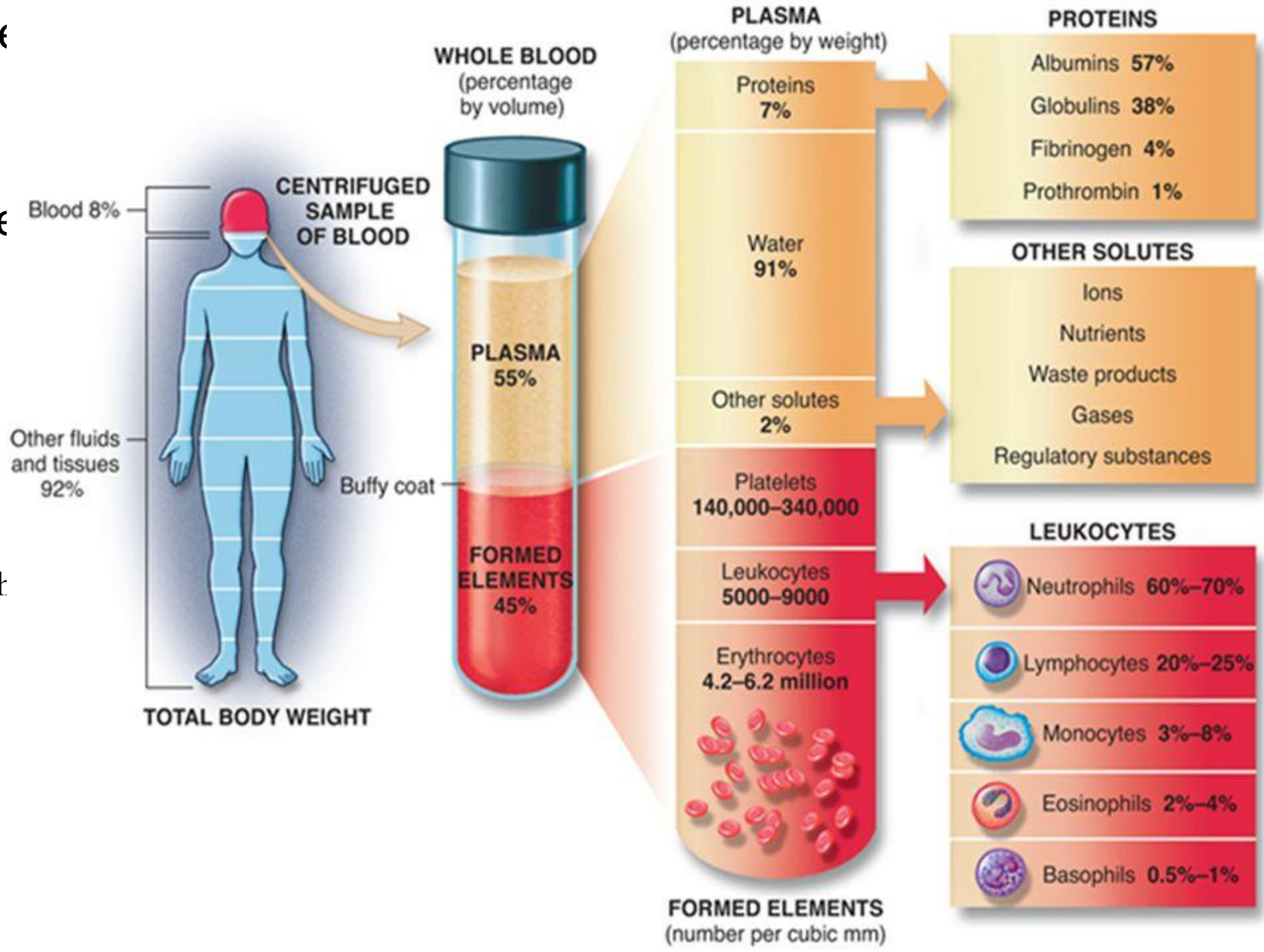
❖Transport

❖Protection – inflammation (protection against infection), WBC (microorganisms, cancer cell and debris), Antibodies (neutralize toxins and destroy pathogens) , platelets (initiate blood clotting, tissue growth and blood vessel maintenance)

❖Regulation – pH, body fluid and blood flow

Blood components and properties

- It is a liquid connective tissue composed of cell and ECM. Here ECM is called plasma.
- Suspension in the plasma are called formed cells. That is cells and cells fragments.
- Formed cells include RBC, WBC and platelets
- Hematocrit (The percentage of total blood volume occupied by RBCs is called th **haematocrit**): 37%-52%
- Anemia and polycythemia
- Buffy coat : 1%
- Plasma : 47-63%



Plasma

- It consists of water, protein, nutrients, electrolytes, nitrogenous wastes , hormones and gases.
- Plasma – blood clots and solids = serum
- Plasma proteins: albumin, globulins and fibrinogen. Functions: clotting, defense, transport of solutes like iron, copper, lipids and hydrophobic hormones.
- Liver produces as much as 4g of plasma protein per hour except gamma globulin (B lymphocytes)

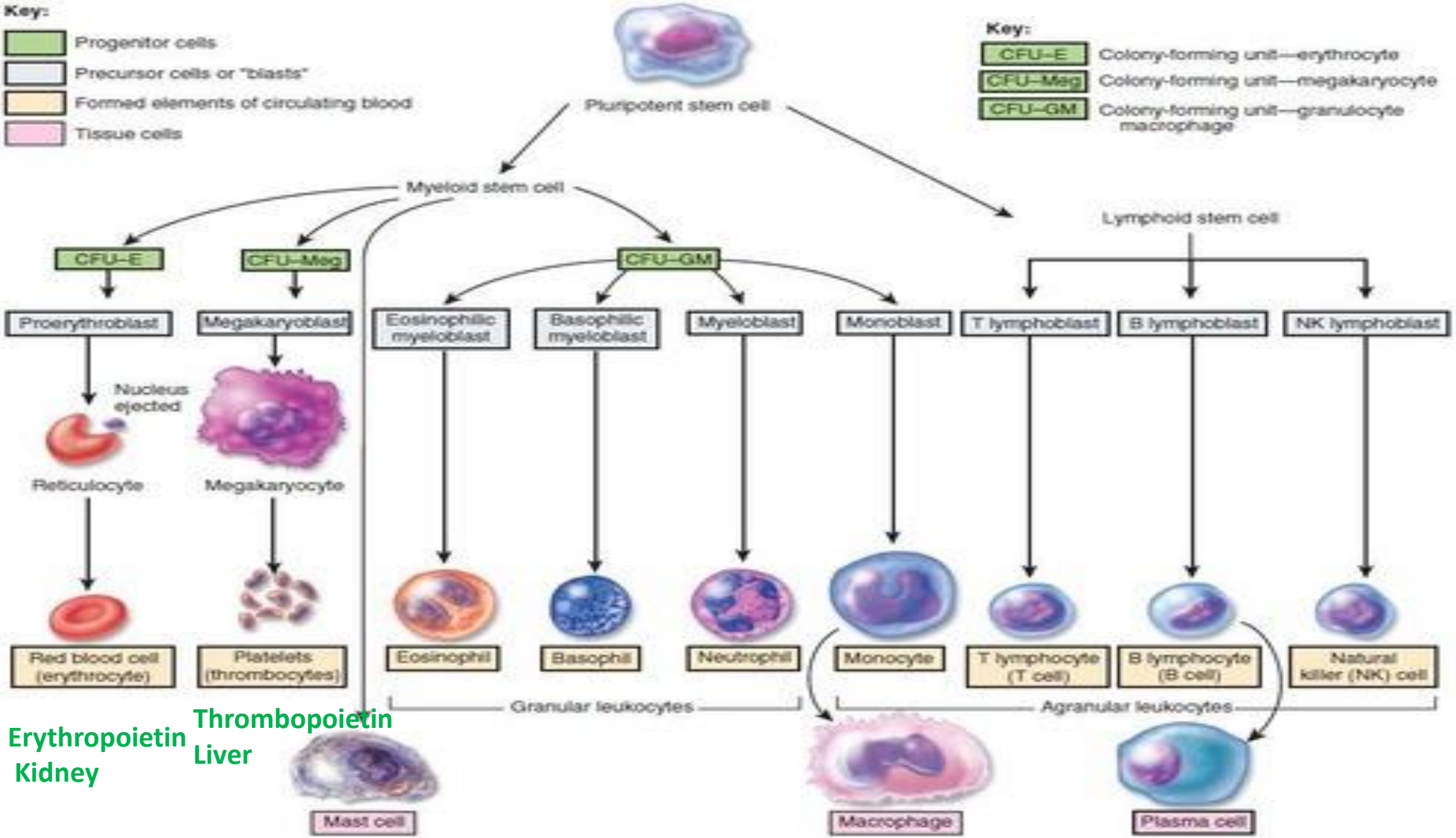
TABLE 18.3 Major Proteins of the Blood Plasma

Proteins	Functions
Albumin (60%)*	Responsible for colloid osmotic pressure; major contributor to blood viscosity; transports lipids, hormones, calcium, and other solutes; buffers blood pH
Globulins (36%)*	Transport and defense functions as itemized below
Alpha (α) globulins	
Haptoglobulin	Transports hemoglobin released by dead erythrocytes
Ceruloplasmin	Transports copper
Prothrombin	Promotes blood clotting
Others	Transport lipids, fat-soluble vitamins, and hormones
Beta (β) globulins	
Transferrin	Transports iron
Complement proteins	Aid in destruction of toxins and microorganisms
Others	Transport lipids
Gamma (γ) globulins	Antibodies; combat pathogens
Fibrinogen (4%)*	Becomes fibrin, the major component of blood clots

*Mean percentage of the total plasma protein by weight

TABLE 19.1 Substances in Blood Plasma

CONSTITUENT	DESCRIPTION	FUNCTION
Water (91.5%)	Liquid portion of blood.	Solvent and suspending medium. Absorbs, transports, and releases heat.
Plasma Protiens (7%)	Most produced by liver.	Responsible for colloid osmotic pressure. Major contributors to blood viscosity. Transport hormones (steroid), fatty acids, and calcium. Help regulate blood pH.
Albumin	Smallest and most numerous plasma proteins.	Help maintain osmotic pressure, an important factor in the exchange of fluids across blood capillary walls.
Globulin	Large proteins (plasma cells produce immunoglobulins).	Immunoglobulins help attack viruses and bacteria. Alpha and beta globulins transport iron, lipids, and fat-soluble vitamins.
Fibrinogen	Large protein.	Plays essential role in blood clotting.
Other solutes (1.5%)		
Electrolytes	Inorganic salts; positively charged (cations) Na^+, K^+, Ca^{2+}, Mg^{2+}; negatively charged (anions) Cl^-, HPO_4^{2-}, SO_4^{2-}, HCO_3^-.	Help maintain osmotic pressure and play essential roles in cell functions.
Nutrients	Products of digestion, such as amino acids, glucose, fatty acids, glycerol, vitamins, and minerals.	Essential roles in cell functions, growth, and development.
Gases	Oxygen (O_2).	Important in many cellular functions.
	Carbon dioxide (CO_2).	Involved in the regulation of blood pH.
	Nitrogen (N_2).	No known function.
Regulatory substances	Enzymes.	Catalyze chemical reactions.
	Hormones.	Regulate metabolism, growth, and development.
	Vitamins.	Cofactors for enzymatic reactions.
Waste Products	Urea, uric acid, creatine, creatinine, bilirubin, ammonia.	Most are breakdown products of protein metabolism that are carried by the blood to organs of excretion.

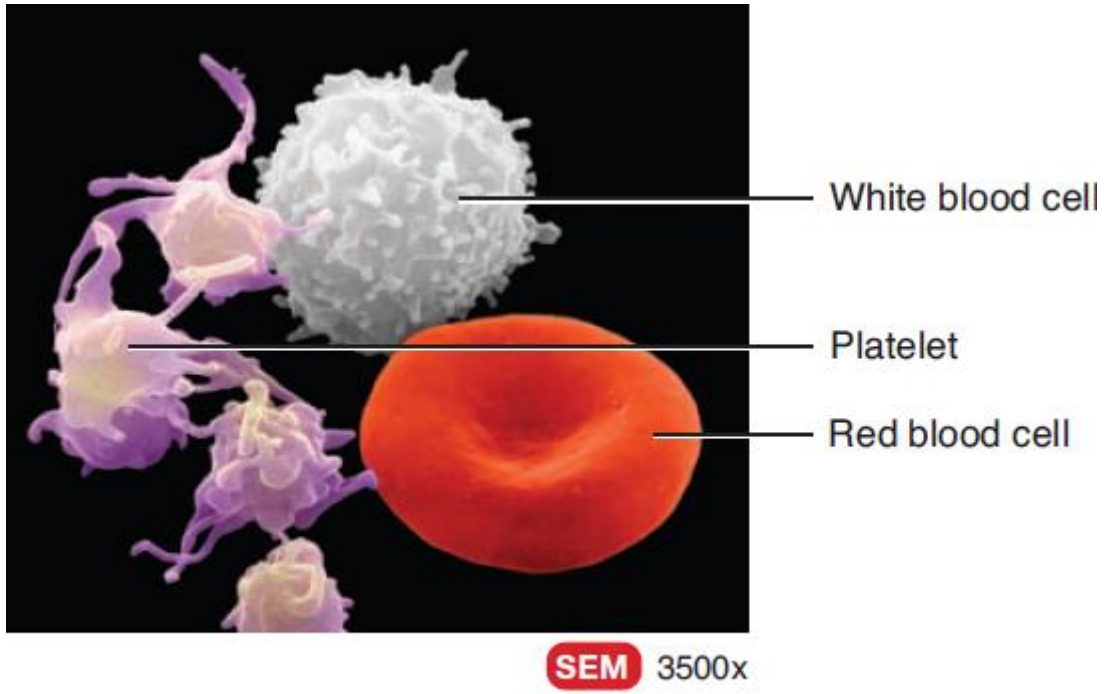


Erythropoietin
Kidney

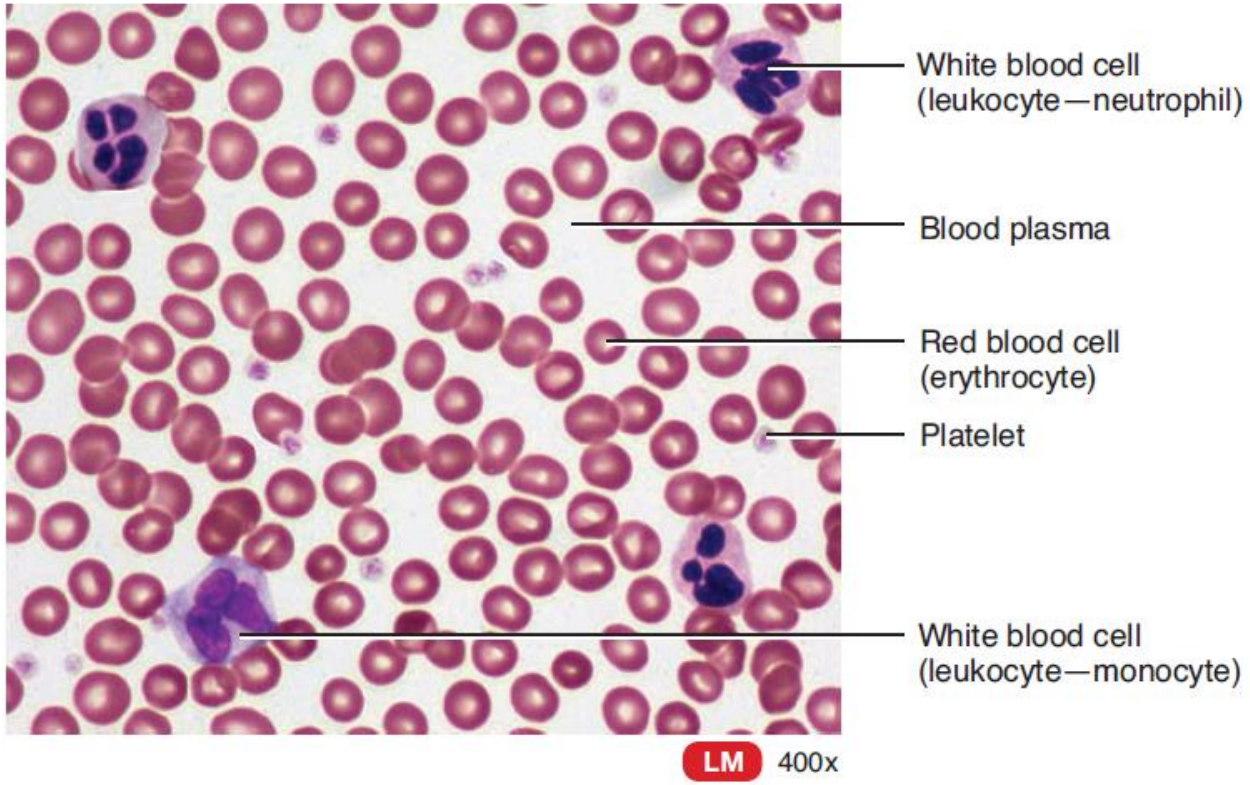
Thrombopoietin
Liver

Hemopoiesis : production of blood

Formed blood cells



(a) Scanning electron micrograph

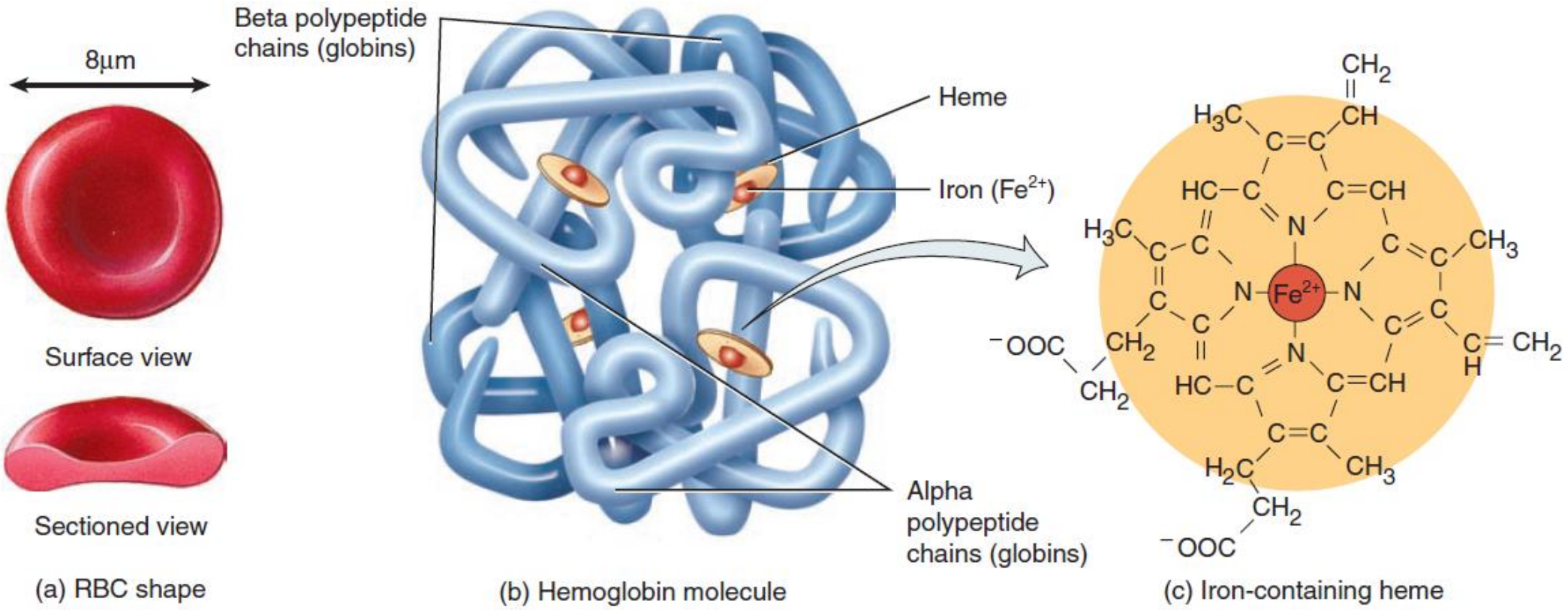


(b) Blood smear

RBC

- **Red blood cells (RBCs)** or **erythrocytes** contain the oxygen-carrying protein **hemoglobin,** which is a pigment that gives whole blood its red color.
- A healthy adult male has about 5.4 million red blood cells per microliter (L) of blood,* and a healthy adult female has about 4.8 million. (One drop of blood is about 50 μL.)
- To maintain normal numbers of RBCs, new mature cells must enter the circulation at the astonishing rate of at least 2 million per second, a pace that balances the equally high rate of RBC destruction.
- RBCs are biconcave discs with a diameter of 7–8 μ m. This gives better surface area and facilitate exchange of gases.
- Their plasma membrane is both strong and flexible, which allows them to deform without rupturing as they squeeze through narrow capillaries.
- RBC lacks most organelle (even nucleus), generate ATP anaerobically.
- Each RBC contains about 280 million hemoglobin molecules. A hemoglobin molecule consists of a protein called **globin,** composed of four polypeptide chains (two alpha and two beta chains); a ringlike nonprotein pigment called a **heme** is bound to each of the four chains.
- At the center of each heme ring is an iron ion (Fe2) that can combine reversibly with one oxygen molecule, allowing each hemoglobin molecule to bind four oxygen molecules.

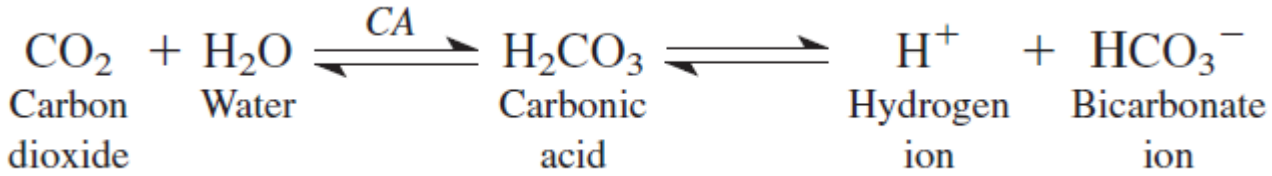
Structure of RBC



Specific functions of RBC

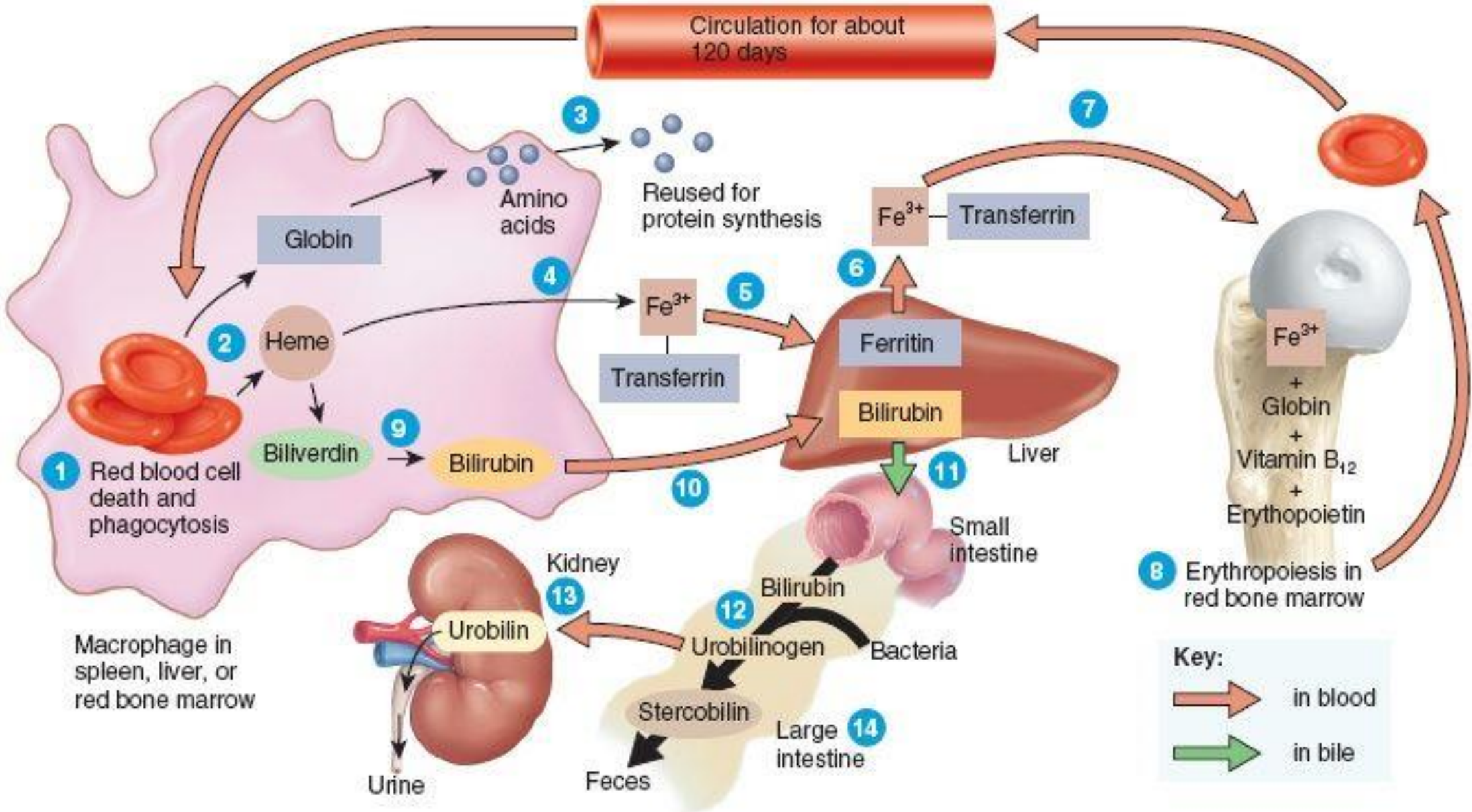
- Carrying O2.

- Red blood cells also contain the enzyme carbonic anhydrase (CA). It serve 2 purpose: 1. Carry CO2 and second work as buffer.

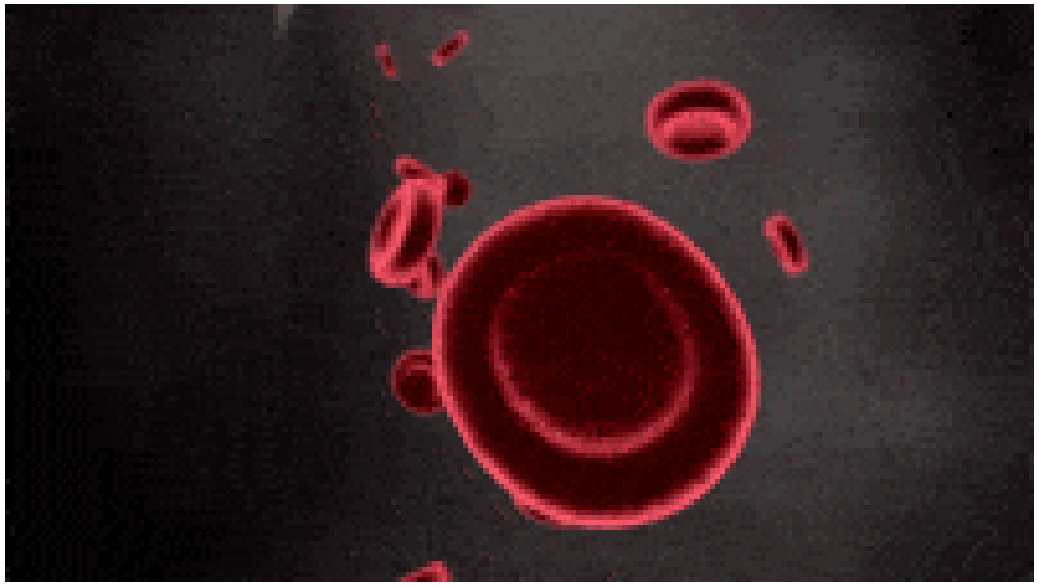


- Contains haemoglobin, which has binding capacity with CO2 (23%) and NO.

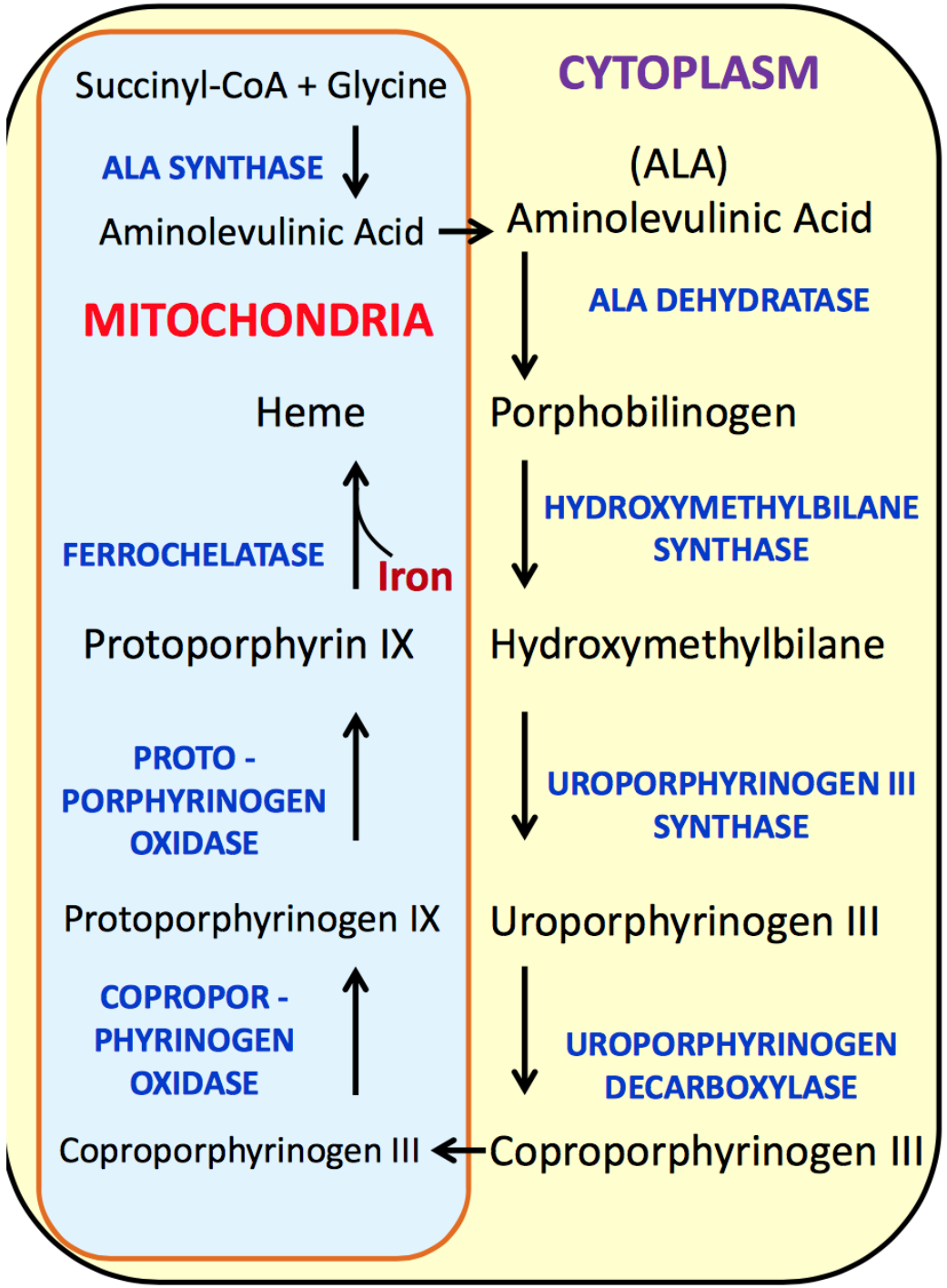
RBC life cycle



Squeezing action of RBC



Heme biosynthesis



Major **sites** of synthesis in the body:

- **Bone marrow erythroid cells** : about **85%** of heme produced in the body. Synthesis rate is **relatively constant** at all times
- **Liver (~10%)**: where **cytochrome P450** is synthesized. Synthesis is up-regulated in response to drug/alcohol metabolism

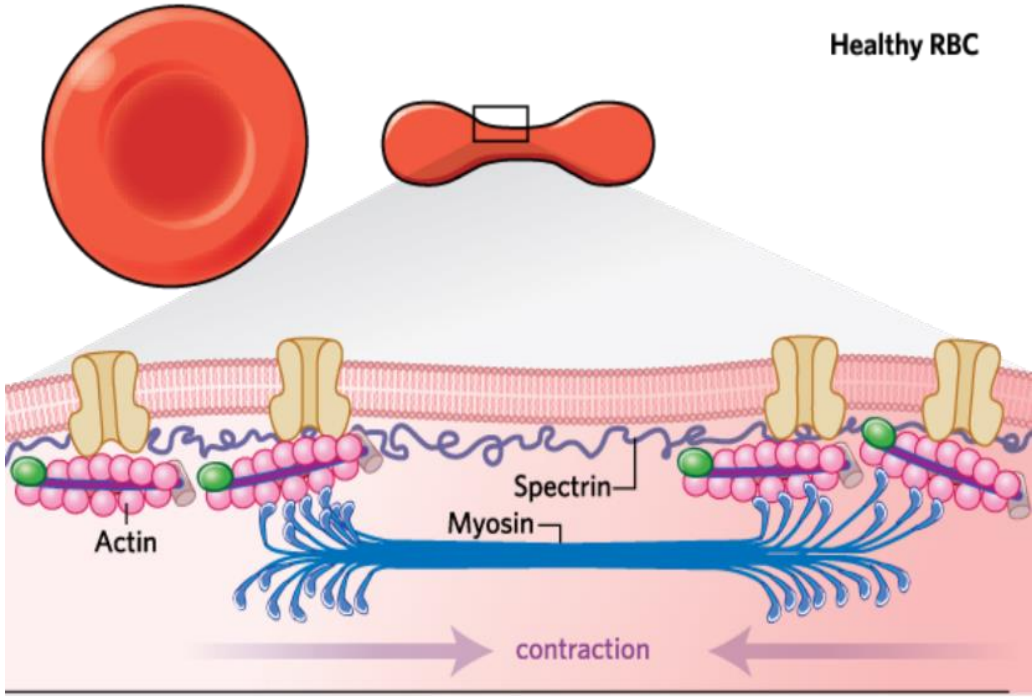
Cellular location:

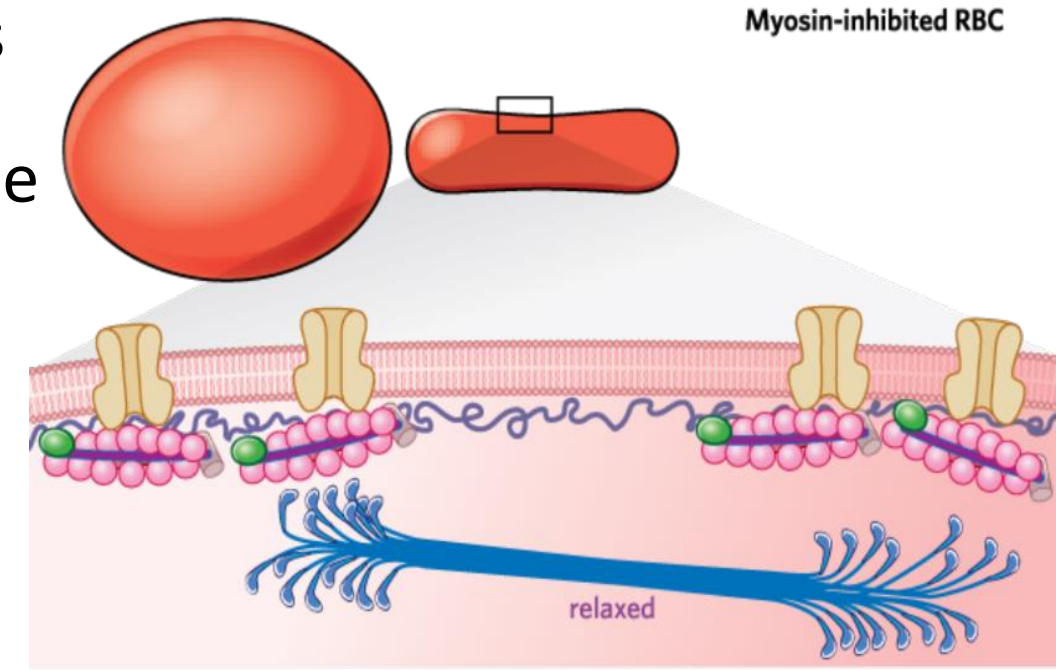
- **Mitochondria**: the initial reaction and the last three steps
- **Cytosol**: the intermediate 4 steps

Note: mature RBCs don't have a mitochondria and cannot make heme

Red Blood Cells

- Normal range: 4 to 5.5 millions per cu mm of blood.
- Shape: Biconcave or disk shaped, helps in rapid diffusion of oxygen and other substances, large surface area, offer minimal tension and can be easily squeeze.
- Structure: non-nucleated, for energy it depends upon glycolytic process, does not have insulin receptor, have special type of cytoskeleton made up of actin and spectrin. Both are attached to transmembrane proteins via Ankyrin protein.
- Absence of spectrin called spherocytosis.
- Rouleaux formation
- Packed cell volume





ROULEAUX EFFECT

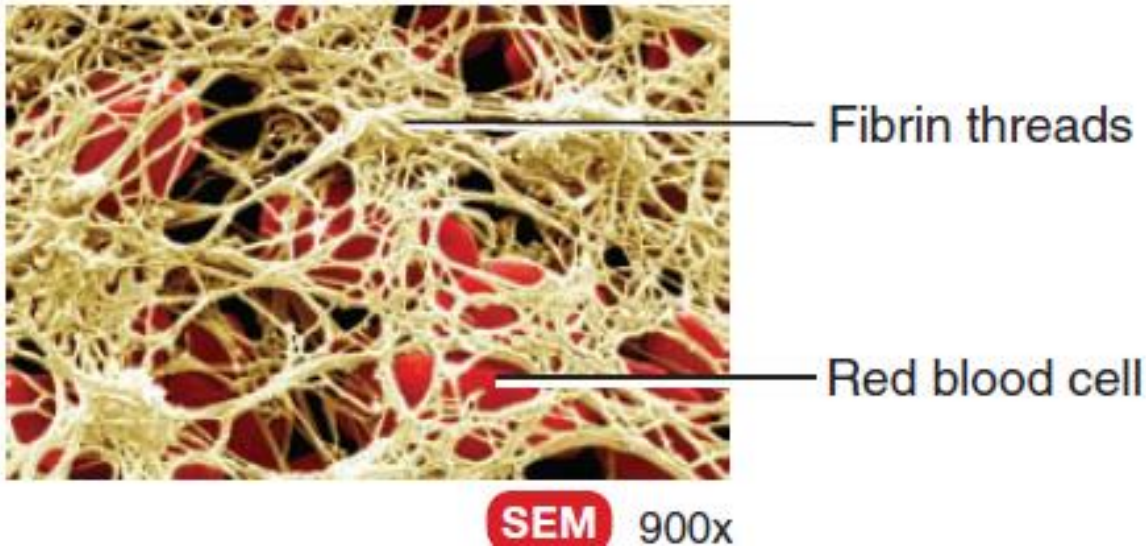
Stacking of Red Blood Cells

Functions of RBCs

- Transport of oxygen and carbon dioxide
- Buffering action
- Blood group determination
- Physiological Variations : increase in RBC: age, gender, high altitude, exercise, emotional conditions increased temperature and after meals.
- Decrease in RBCs: high barometric pressure, During sleep
- Physiological variations: polycythemia and Anemia

Blood clotting

- Normally, blood remains in its liquid form as long as it stays within its vessels. If it is drawn from the body, however, it thickens and forms a gel.
- Eventually, the gel separates from the liquid. The straw-colored liquid, called **serum,** is simply blood plasma
- minus the clotting proteins. The gel is called a **clot.**
- It consists of a network of insoluble protein fibers called fibrin in which the formed elements of blood are trapped.
- Thrombosis – fast coagulation
- Haemorrhage – No blood clotting



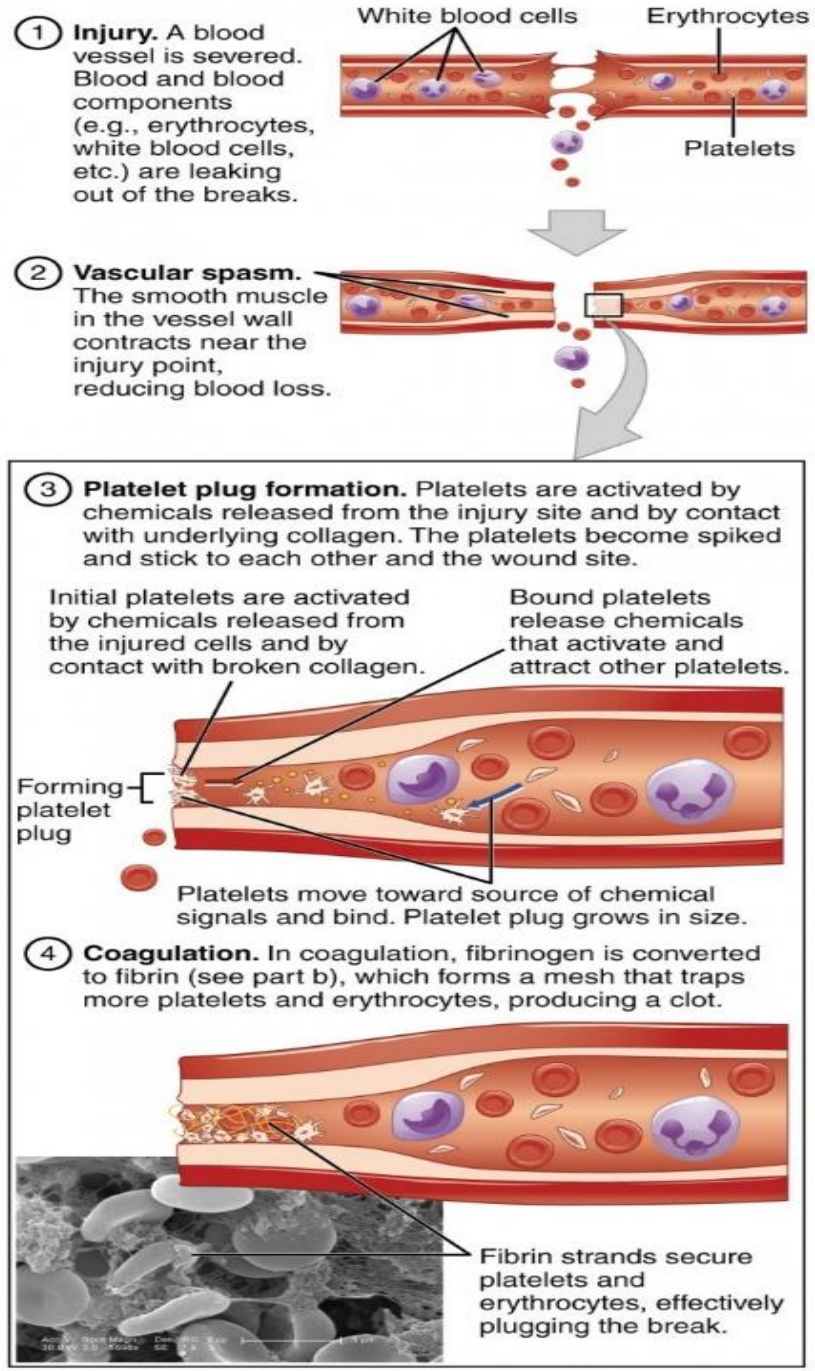
Blood clotting or coagulation

Three steps of blood clotting:

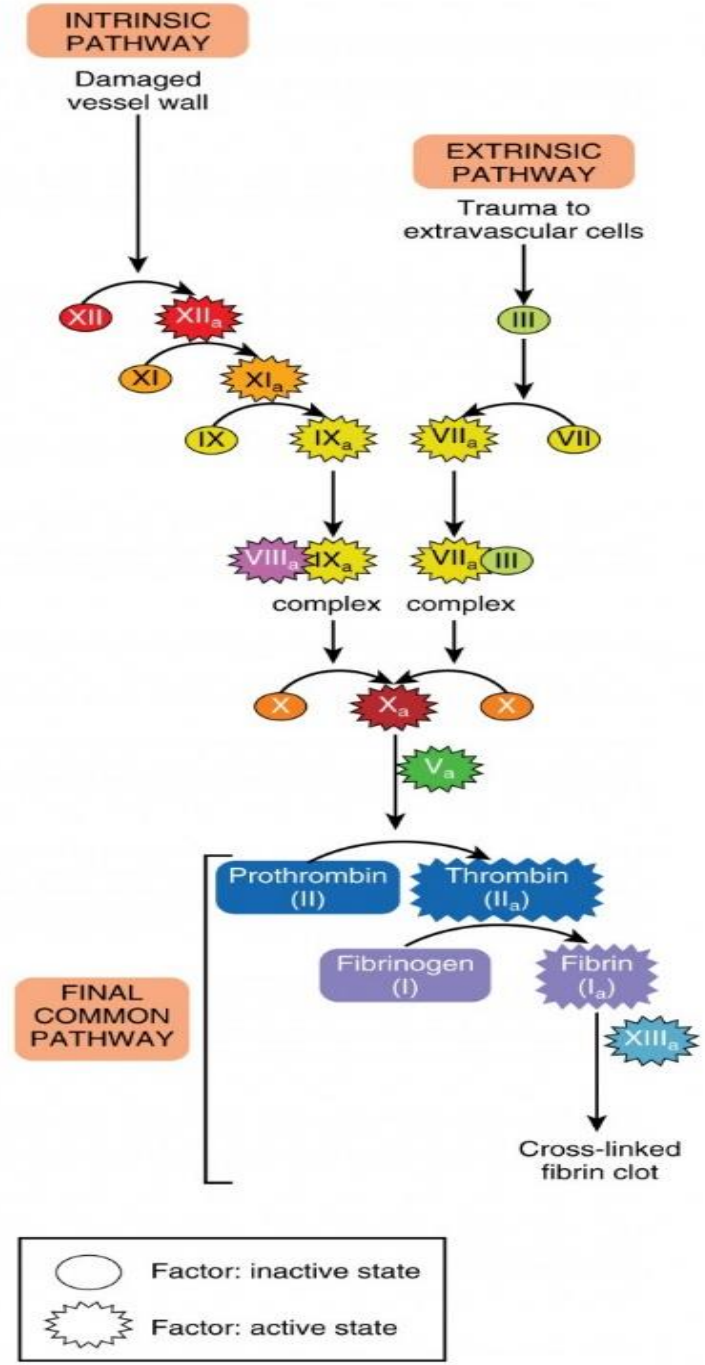
1. Formation of prothrombin activator
2. Conversion of prothrombin into thrombin
3. Conversion of fibrinogen into fibrin

CLOTTING FACTORS

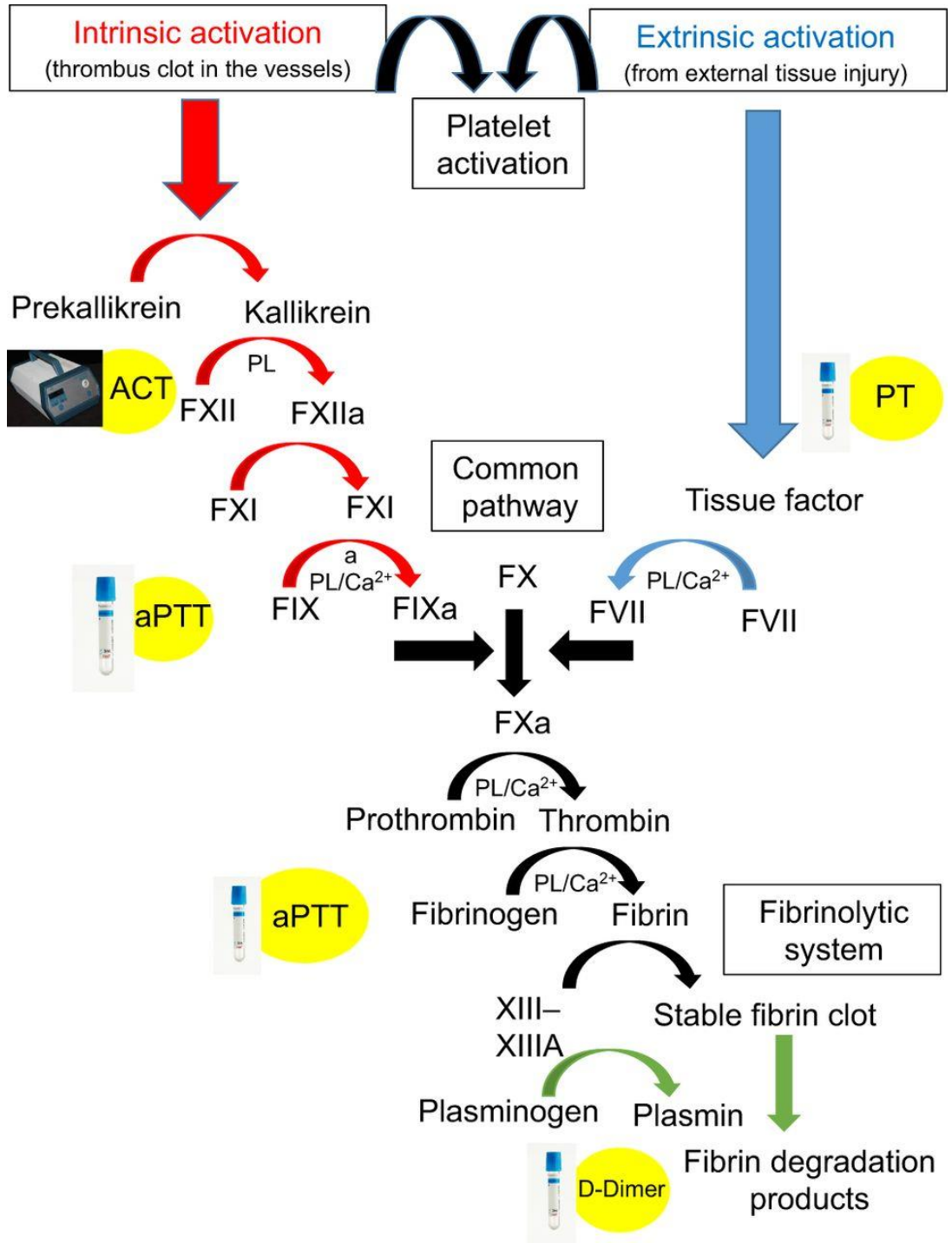
Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue Thromboplastin
Factor IV	Calcium Ions
Factor V	Labile Factor
Factor VII	Stable Factor
Factor VIII	Antihemophilic Factor
Factor IX	Christmas Factor, or Plasma Thromboplastin Component (PTC)
Factor X	Stuart-Prower Factor
Factor XI	Plasma Thromboplastin Antecedent (PTA)
Factor XII	Hageman Factor
Factor XIII	Fibrin Stabilizing Factor



(a) The general steps of clotting

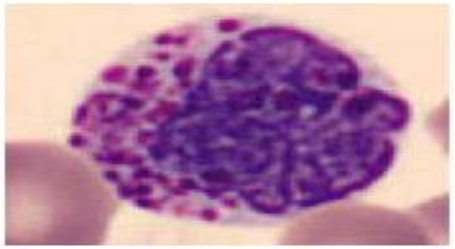
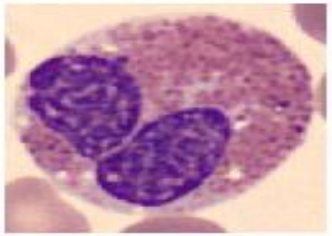
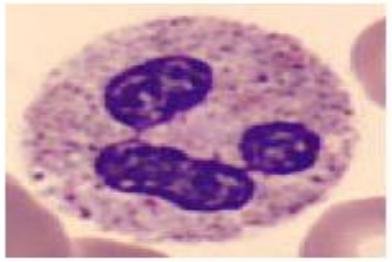
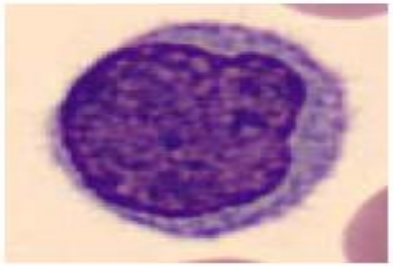
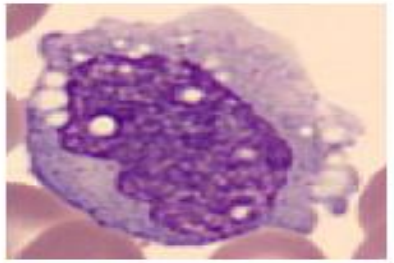


(b) Fibrin synthesis cascade


Intrinsic activation
(thrombus clot in the vessels)
Extrinsic activation
(from external tissue injury)
Platelet activation
Prekallikrein
Kallikrein
PL
ACT
FXII
FXIIa
PT
FXI
FXI
Common pathway
Tissue factor
a
PL/Ca2+
FX
PL/Ca2+
aPTT
FIX
FIXa
FVII
FVII
FXa
PL/Ca2+
Prothrombin
Thrombin
PL/Ca2+
aPTT
Fibrinogen
Fibrin
Fibrinolytic system
XIII–
XIIIA
Stable fibrin clot
Plasminogen
Plasmin
D-Dimer
Fibrin degradation products

White blood cells

- WBCs or Leukocytes are colorless and nucleated formed elements of blood.
- Compared to RBCs, WBCs are larger in size and smaller in number.
- They play an important role in defense mechanism of body and protect it from invading organisms.
- Major difference in terms of : larger size, irregular shape, nucleated, many types, short life span and present of granules.
- Classifications: granulocytes and a granulocytes.
- Normal WBC count : 4000 to 11000/cu mm of blood.
- Leukocytosis and leukopenia. Leukemia

Type	Granulocytes			Agranulocytes	
	Basophil	Eosinophil	Neutrophil	Lymphocyte	Monocyte
Microscopic image					
Approx. % in adults	0.4	2.3	62	30	5.3
Diameter (μm)	10–16	9–15	9–15	Small lymphocytes 7–8 Large lymphocytes 12–18	12–20

Acidic stain: when stain pink or red with eosin

Basic stain: stain purple blue with methylene blue.

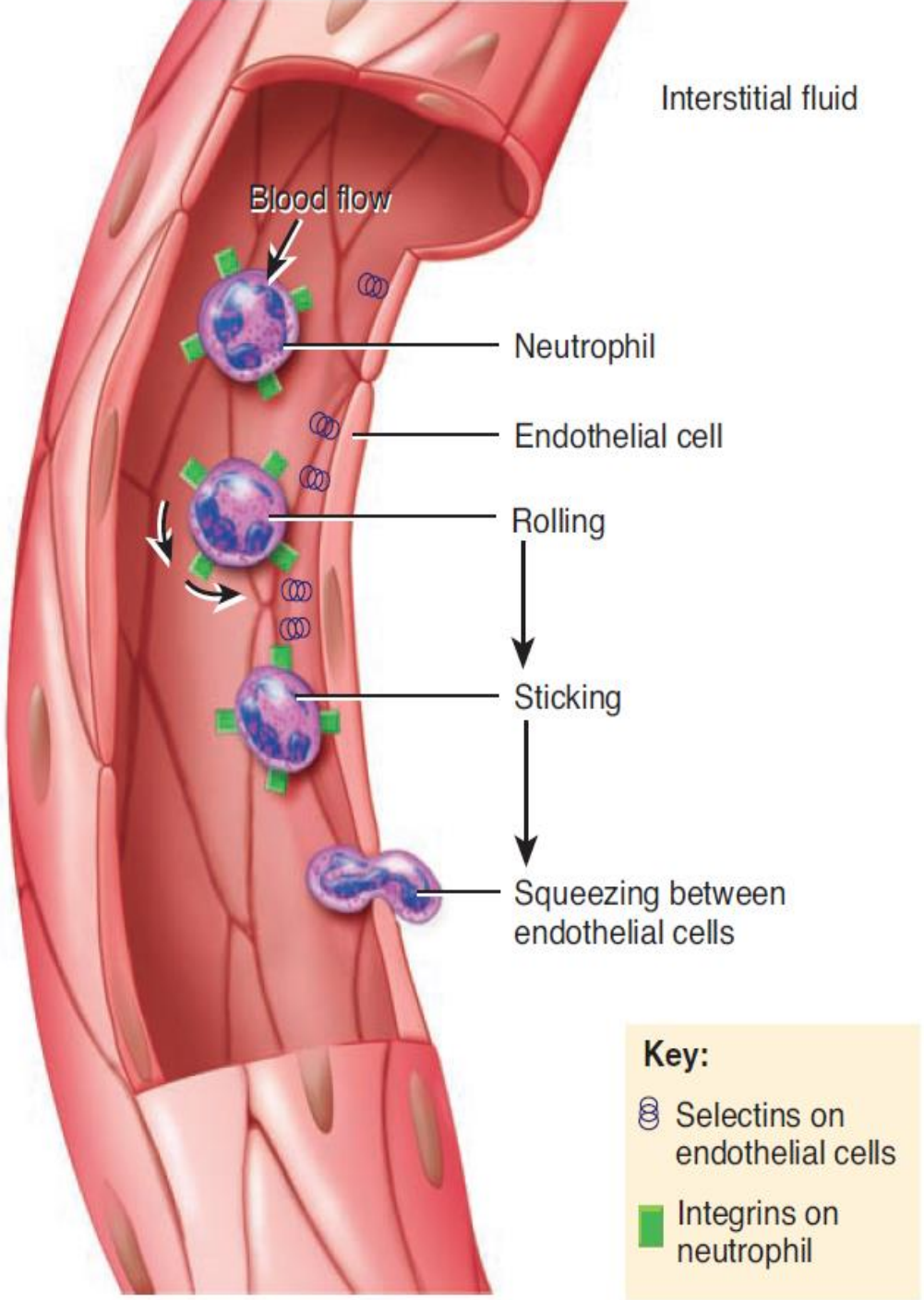
Based on functions lymphocytes are divided into 2 groups: T lymphocytes and B lymphocytes

White blood cells and all other nucleated cells in the body have proteins, called **major histocompatibility (MHC) antigens,** protruding from their plasma membrane into the extracellular fluid.

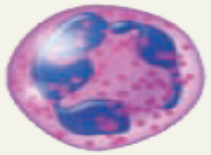
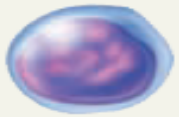
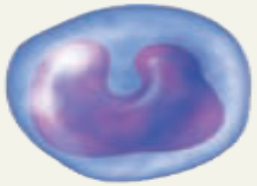
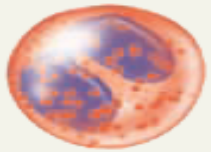
These "cell identity markers" are unique for each person (except identical twins). Although RBCs possess blood group antigens, they lack the MHC antigens.

Few things

- **Leukocytosis**, an increase in the number of WBCs above 10,000/L, is a normal, protective response to stresses such as invading microbes, strenuous exercise, anesthesia, and surgery.
- An abnormally low level of white blood cells (below 5000/L) is termed **leukopenia.** It is never beneficial and may be caused by radiation, shocl and certain chemotherapeutic agents.
- To kill any pathogens, many WBCs leave the bloodstream and collect at sites of pathogen invasion or inflammation. Once granular leukocytes ar monocytes leave the bloodstream to fight injury or infection, they never return to it.
- Lymphocytes, on the other hand, continually recirculate from blood to interstitial spaces of tissues to lymphatic fluid and back to blood. Only 2% of the total lymphocyte population is circulating in the blood at any given time; the rest is in lymphatic fluid and organs such as the skin, lungs, lymph nodes, and spleen.
- RBCs are contained within the bloodstream, but WBCs leave the bloodstream by a process termed **emigration**, also called *diapedesis*, in which they roll along the endothelium, stick to it, and then squeeze between endothelial cells.
- Several different chemicals released by microbes and inflamed tissues attract phagocytes, a phenomenon called **chemotaxis.**



WBC

WBC TYPE	HIGH COUNT MAY INDICATE	LOW COUNT MAY INDICATE
Neutrophils 	Bacterial infection, burns, stress, inflammation.	Radiation exposure, drug toxicity, vitamin B_{12} deficiency, systemic lupus erythematosus (SLE).
Lymphocytes 	Viral infections, some leukemias.	Prolonged illness, immunosuppression, treatment with cortisol.
Monocytes 	Viral or fungal infections, tuberculosis, some leukemias, other chronic diseases.	Bone marrow suppression, treatment with cortisol.
Eosinophils 	Allergic reactions, parasitic infections, autoimmune diseases.	Drug toxicity, stress.
Basophils 	Allergic reactions, leukemias, cancers, hypothyroidism.	Pregnancy, ovulation, stress, hyperthyroidism.

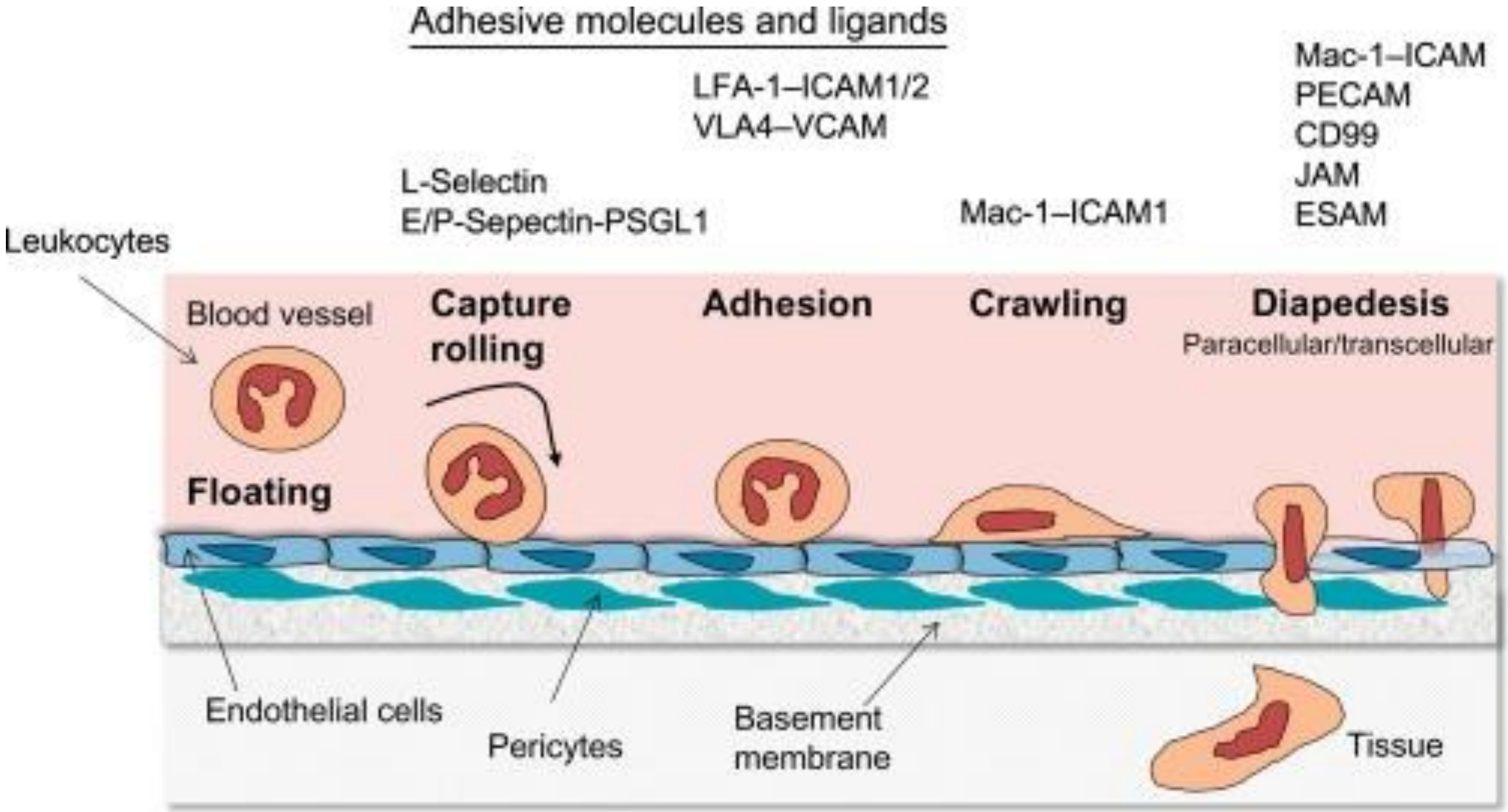
White blood cells (WBC)

Specific WBC	Function	Deferential %
Neutrophil	General phagocytosis: acute bacterial infections	54-62%
Eosinophil	Kills parasites, allergic condition	1-3 %
Basophil	Release heparin and histamine	< 1%
Monocyte	Phagocytosis of large particles in typhoid, malaria	3-9%
Lymphocyte	Produce antibody	25-33%

TABLE 18.1 Summary of Formed Elements of the Blood

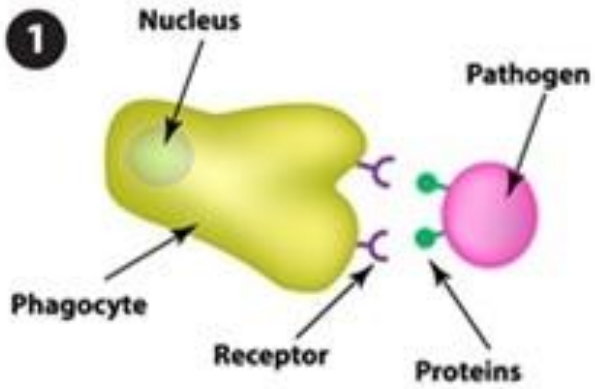
Cell Type	Illustration	Description*	Number of Cell per mm^3 (µl) of Blood	Duration of Development (D) and Life Span (LS)	Function
ERYTHROCYTES (red blood cells; RBCs)		Biconcave, anucleate disc; salmon-colored; diameter 7–8 µm	4–6 million	D: 5–9 days LS: 100–120 days	Transport oxygen and carbon dioxide
LEUKOCYTES (white blood cells, WBCs)		Spherical, nucleated cells	4800–11,000		
Granulocytes		Nucleus multilobed; inconspicuous cytoplasmic granules; diameter 12–14 µm	3000–7000	D: 7–11 days LS: 6 hours to a few days	Destroy bacteria by phagocytosis
• Neutrophils					
• Eosinophils		Nucleus bilobed; red cytoplasmic granules; diameter 12–15 µm	100–400	D: 7–11 days LS: about 5 days	Turn off allergic responses and kill parasites
• Basophils		Nucleus bilobed; large blue-purple cytoplasmic granules; diameter 10–14 µm	20–50	D: 3–7 days LS: a few hours to a few days	Release histamine and other mediators of inflammation
Agranulocytes		Nucleus spherical or indented; pale blue cytoplasm; diameter 5–17 µm	1500–3000	D: days to weeks LS: hours to years	Mount immune response by direct cell attack (T cells) or via antibodies (B cells)
• Lymphocytes					
• Monocytes		Nucleus U- or kidney-shaped; gray-blue cytoplasm; diameter 14–24 µm	100–700	D: 2–3 days LS: months	Phagocytosis; develop into macrophages in tissues
PLATELETS		Discoid cytoplasmic fragments containing granules; stain deep purple; diameter 2–4 µm	150,000–500,000	D: 4–5 days LS: 5–10 days	Seal small tears in blood vessels; instrumental in blood clotting

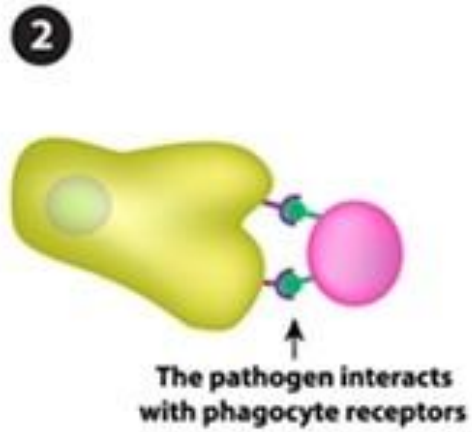
*Appearance when stained with Wright's stain.

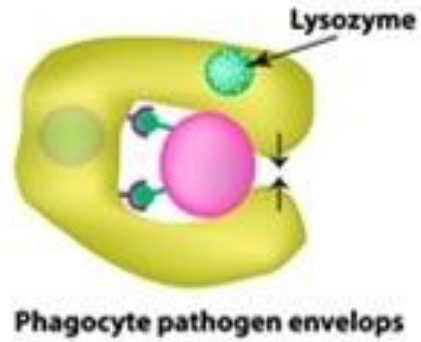

Adhesive molecules and ligands
LFA-1–ICAM1/2
VLA4–VCAM
Mac-1–ICAM
PECAM
CD99
JAM
ESAM
L-Selectin
E/P-Sepectin-PSGL1
Mac-1–ICAM1
Leukocytes
Blood vessel
Capture
rolling
Adhesion
Crawling
Diapedesis
Paracellular/transcellular
Floating
Endothelial cells
Pericytes
Basement
membrane
Tissue

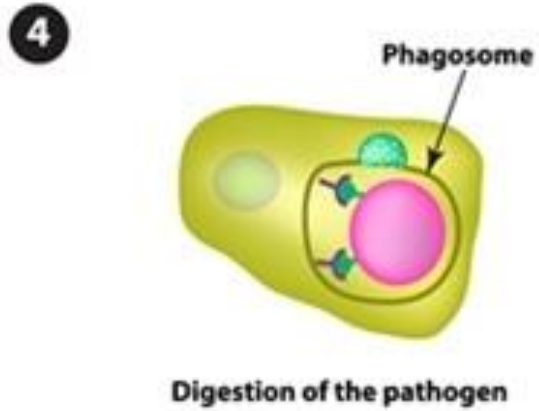
PHAGOCYTOSIS

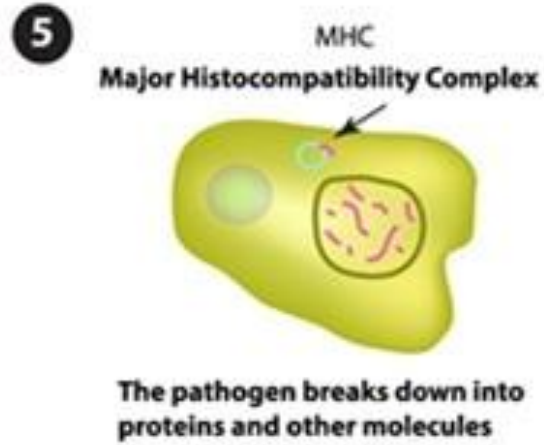
INNATE (NONSPECIFIC) IMMUNITY

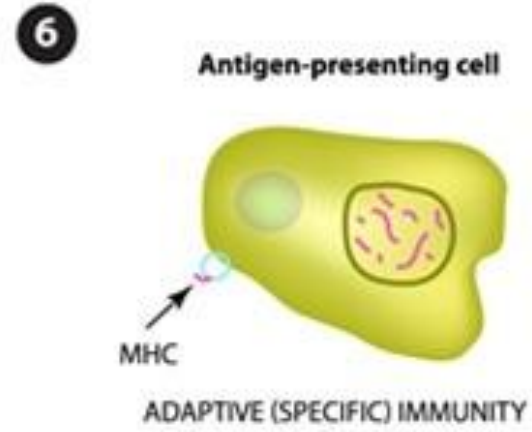












ADAPTIVE (SPECIFIC) IMMUNITY

Video links

- https://youtu.be/W9kGIaGG5Lc