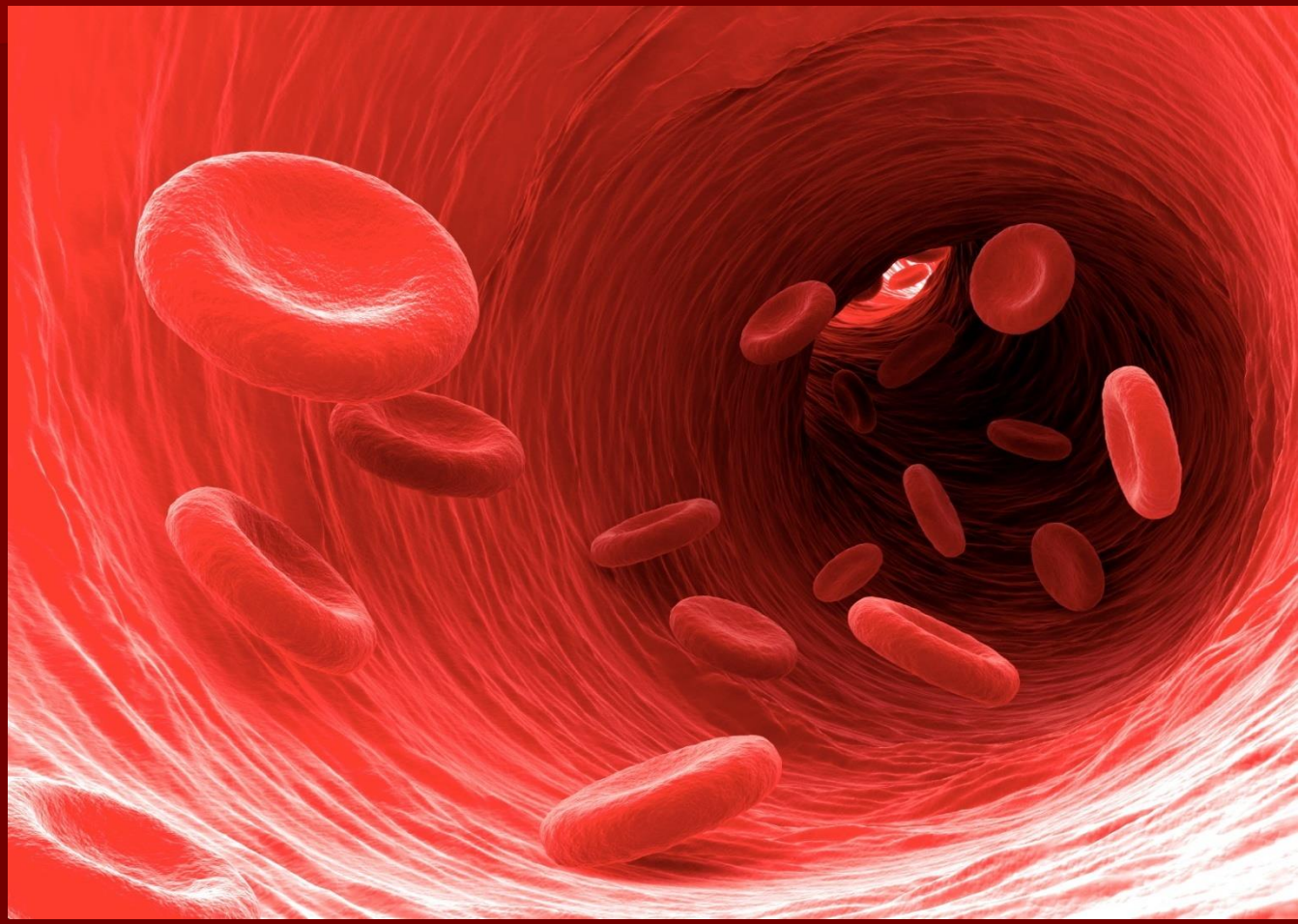
Biochemistry of the blood



Naumov AV.

Ass.prof.

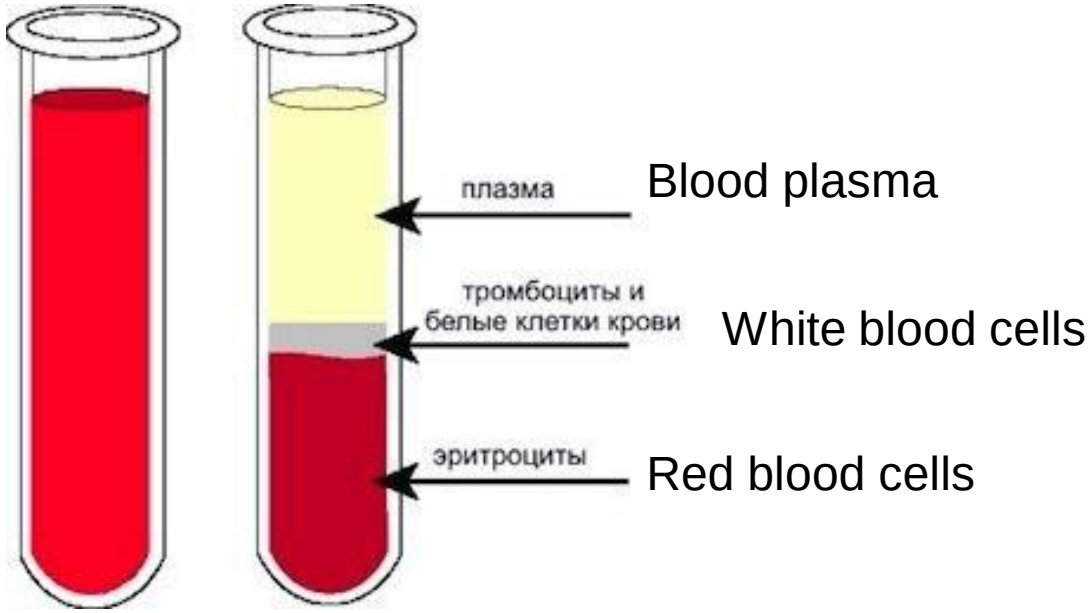
Blood — is a body fluid in humans and other animals that delivers **necessary substances** (nutrients and oxygen) to the cells and transports metabolic waste products away from those same cells.

Human blood constitutes about **8%** of the body's weight.

Consists of ***cells***, ***cell fragments***, ***proteins***

in an aqueous medium - the **blood plasma**.

Blood plasma is separated from the blood by spinning a tube of fresh blood containing an **anticoagulant** in a centrifuge until the blood cells fall to the bottom of the tube.



Blood serum is blood plasma without **clotting factors**.

Blood plasma

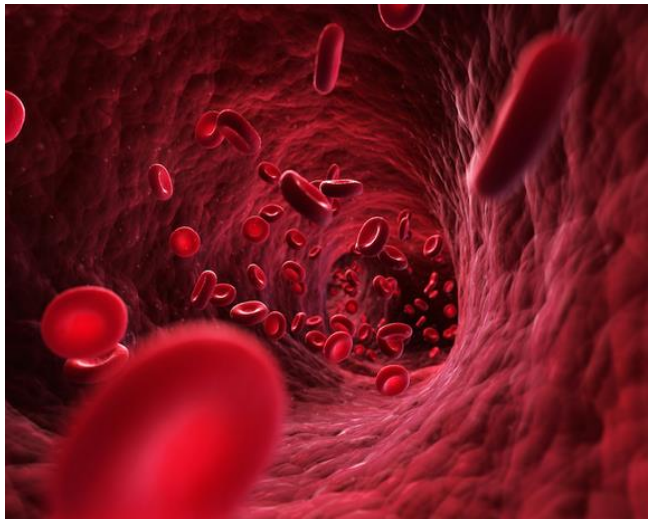
- is a yellowish coloured **liquid component** of blood;
- it is the **intravascular fluid** part of **extracellular fluid**;
- it makes up about **55%** of the body's total blood volume

Contains:

- **water** - up to **92-95%** by volume
- dissolved **proteins** - **6-8%** (serum albumins, globulins, fibrinogen etc).
- **glucose**,
- **clotting factors**,
- **electrolytes** (Na^+, Ca^{2+}, Mg^{2+}, HCO_3^-, Cl^-, etc.)
- **hormones**,
- **carbon dioxide** (plasma being the main medium for excretory product transportation) and **oxygen**.

General characteristics of the blood

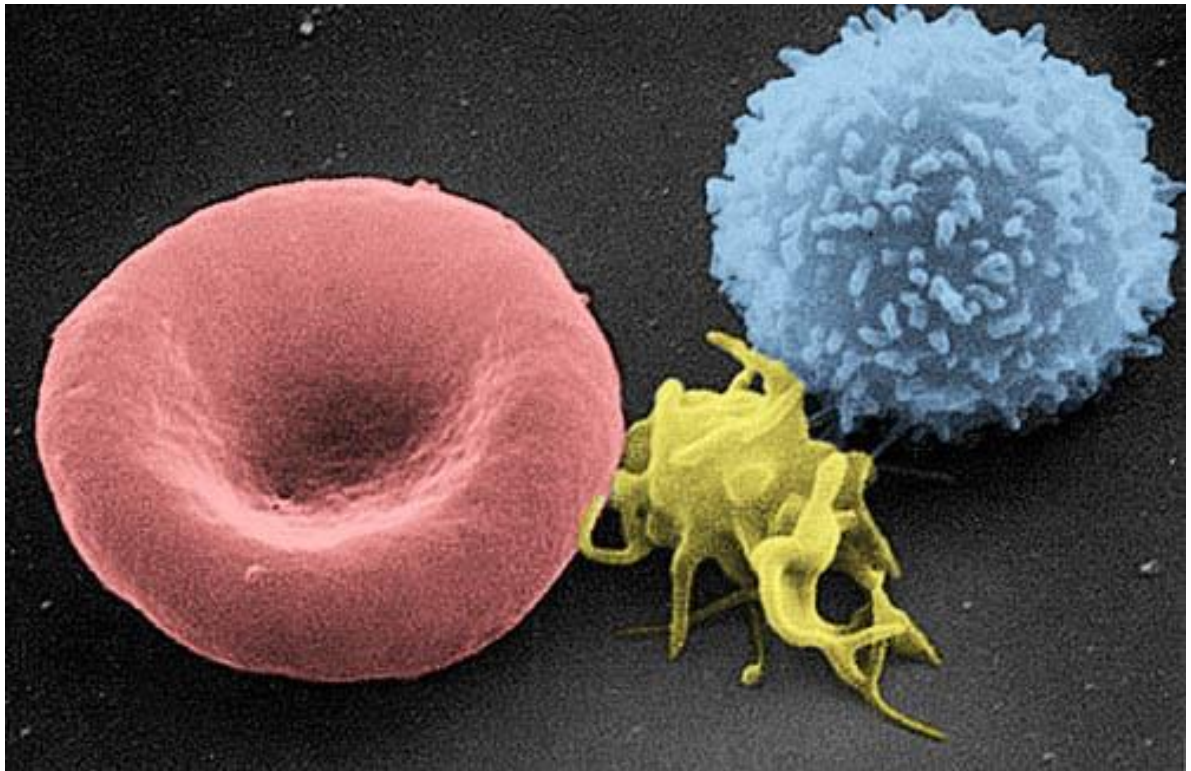
- volume is ~ **5.2 l** in males and ~ **3.9 l** in females
- pH is **7.36-7.42**
- relative density
  - of whole blood is **1.050-1.065**,
  - of plasma **1.024-1.030**



- viscosity is **4-5**-fold that of water
- plasma osmotic pressure is about **7.6** atm
- aqueous solution containing ~ **92%** water, **8%** blood plasma proteins

The **blood cells** are mainly

- **red blood cells** - also called **RBCs** or **erythrocytes**,
- **white blood cells** - also called **WBCs** or **leukocytes** and
- **platelets** - also called **thrombocytes**.



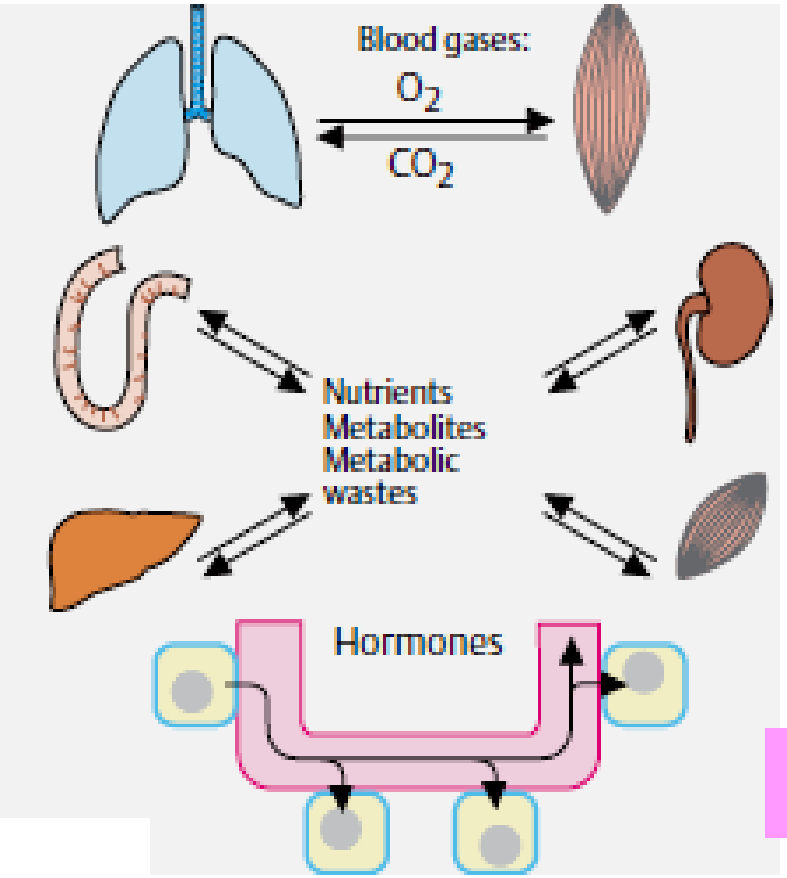
General characteristics of the blood

One microliter of blood contains:

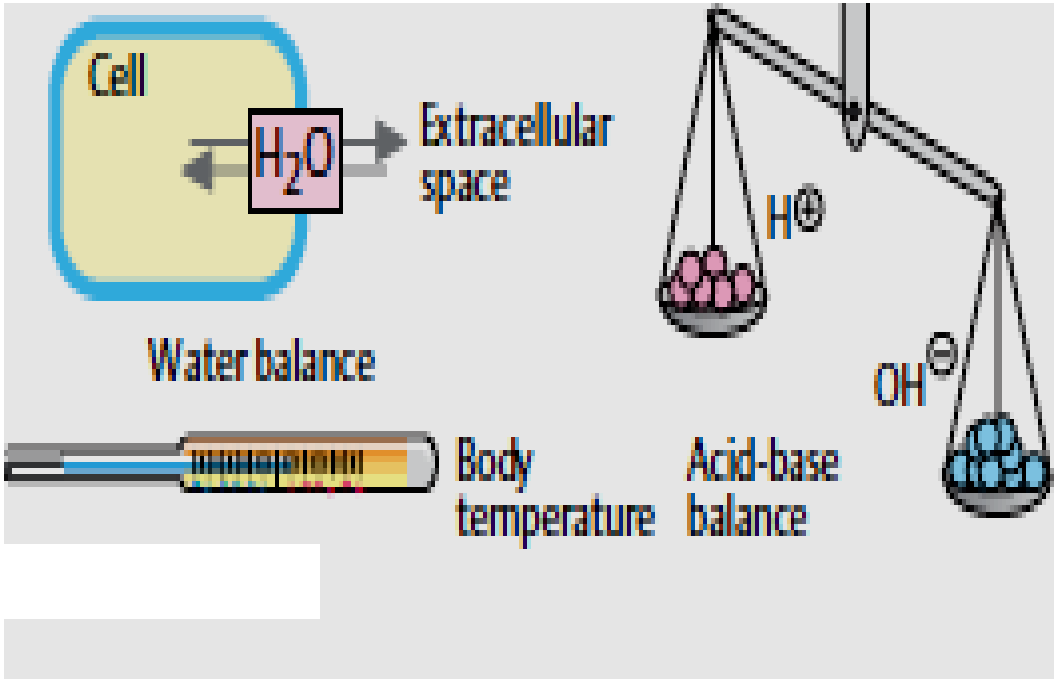
- **Erythrocytes** - **4.7**-**6.1** million (male), **4.2 - 5.4** million (female). RBC contain the blood's **hemoglobin** and distribute **O_2**. The RBC are marked by **glycoproteins** that define the different **blood types**. The proportion of blood occupied by RBC is referred to as the **hematocrit**, and is normally about **45%**.
- **4,000–11,000 leukocytes**. White blood cells are part of the body's **immune system**; they destroy and remove old or aberrant cells and cellular debris, as well as attack infectious agents (**pathogens**) and foreign substances.
- **200,000–500,000 thrombocytes** (platelets), they take part in blood clotting (**coagulation**). **Fibrin** from the coagulation cascade creates a **mesh** over the **platelet plug**.

Major Functions of Blood

1. Transport

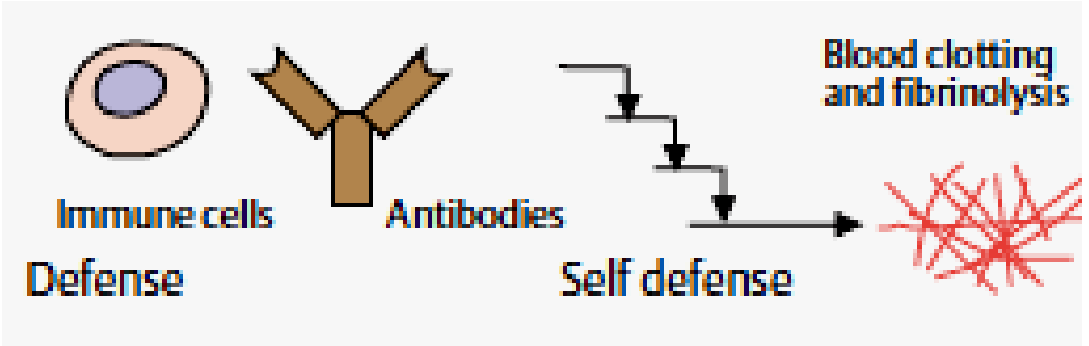


2.Homeostasis



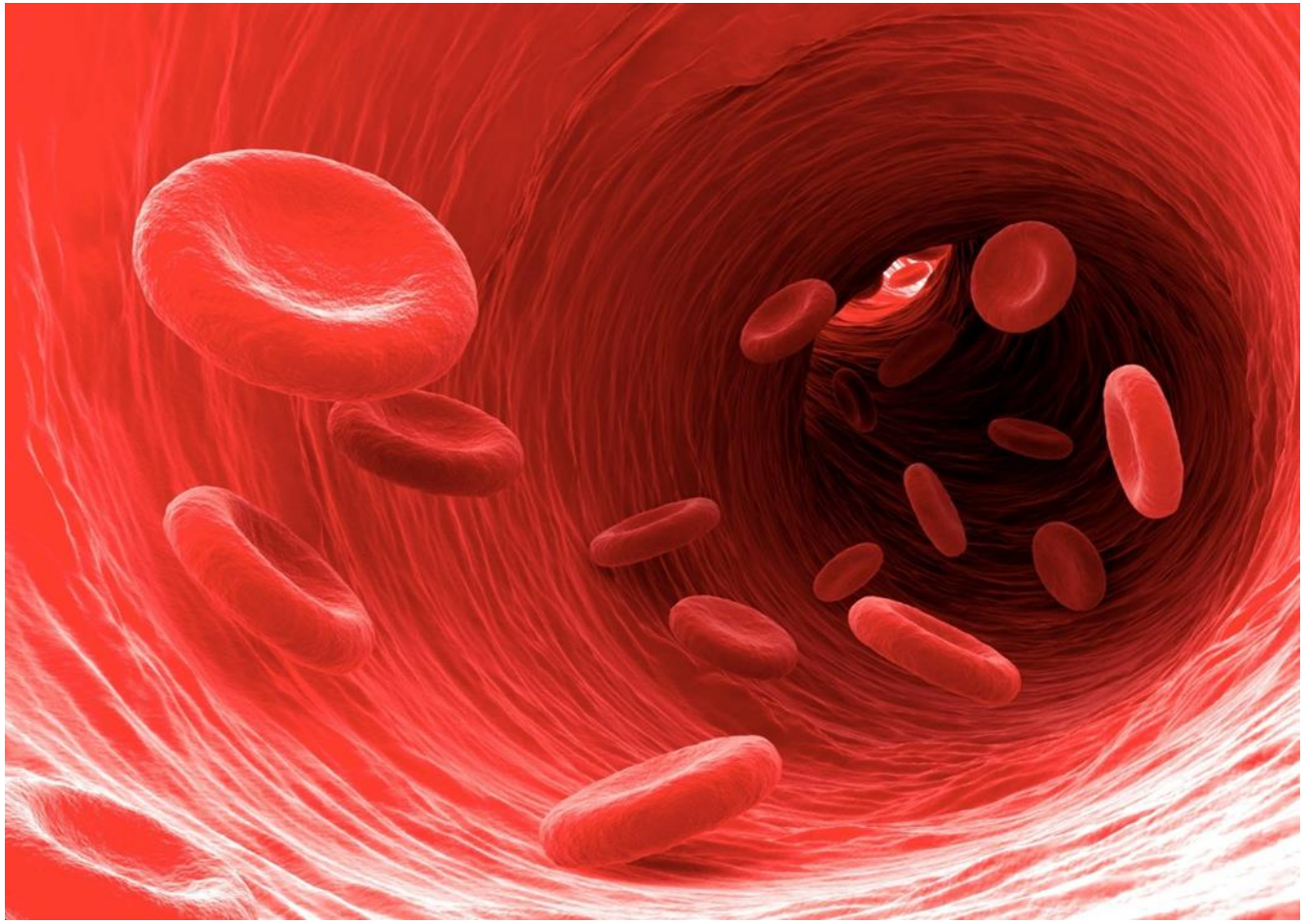
3. Defense

4. Self-protection



Major Functions of Blood

1. **Respiration**—transport of O_2 from the lungs to the tissues and of CO_2 from the tissues to the lungs;
2. **Nutrition**—transport of absorbed food materials;
3. **Excretion**—transport of metabolic waste to the kidneys, lungs, skin, and intestines for removal;
4. **Maintenance** of the normal **acid–base balance**;
5. **Regulation** of **water balance** through the effects of blood on the exchange of water between the circulating fluid and the tissue fluid;
6. **Regulation** of **body temperature** by the distribution of body heat;
7. **Defense** against **infection** by the white blood cells and circulating antibodies;
8. **Transport** of hormones and **regulation** of metabolism;
9. **Transport** of metabolites;
10. **Coagulation**



Red blood cells – erythrocytes

RED BLOOD CELLS DERIVE FROM HEMATOPOIETIC STEM CELLS

Stem cells possess a unique capacity both to produce unaltered daughter cells (**self-renewal**) and to generate a diverse range of specialized cell types (**potency**).

Stem cells therefore can be considered to exist in an undifferentiated state.

Stem cells may be

- totipotent - capable of producing all the cells in an organism,
- pluripotent - able to differentiate into cells of any of the three germ layers,
- multipotent - produce only cells of a closely related family or
- unipotent - produce only one type of cell.

Stem cells are also classified as:

- embryonic;
- adult.

Adult stem cells are more limited in their capacity to differentiate.

RED BLOOD CELLS DERIVE FROM HEMATOPOIETIC STEM CELLS

Differentiation of **hematopoietic stem cells** is regulated by a set of secreted glycoproteins called **cytokines**.

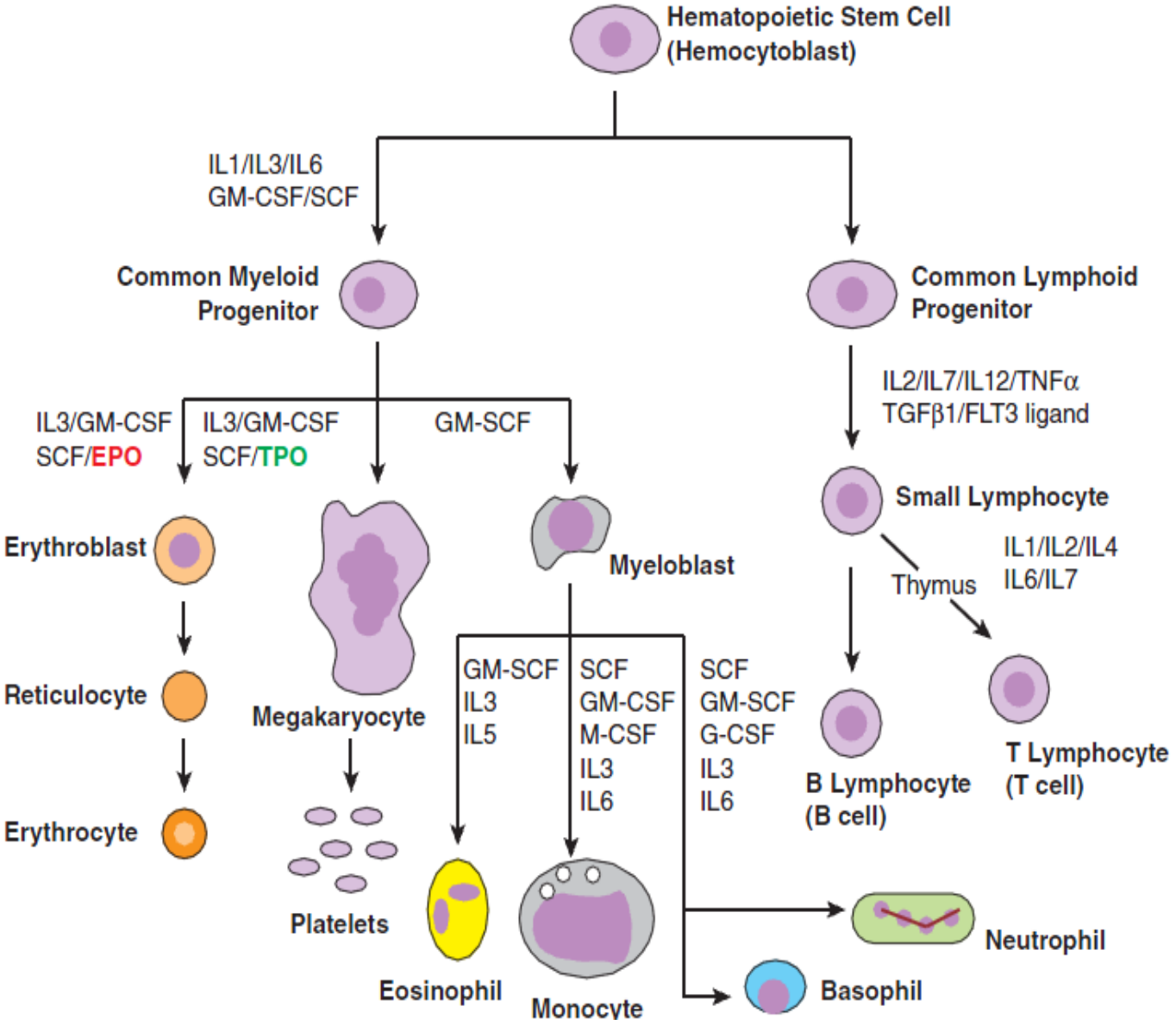
Stem cell factor and several **colony stimulating factors** collaborate with interleukins (IL) -1, -3, and -6 to stimulate the proliferation of hematopoietic **stem cells** in the **bone marrow** and their commitment to differentiate into one of several **myeloid cell types**.

Binding of **erythropoietin** or **thrombopoietin** directs **myeloid progenitor cells** to eventually differentiate into **erythrocytes** or **platelets**, respectively.

Hematopoiesis.

The paths by which hematopoietic stem cells differentiate to produce many of the more quantitatively prominent **red** and **white blood** cells.

IL, interleukin;
SCF, stem cell factor;
G-CSF, granulocyte-colony stimulating factor;
M-CSF, macrophage-colony stimulating factor;
GM-CSF, granulocyte macrophage-colony stimulating factor;



EPO, erythropoietin; **TPO**, thrombopoietin

Specific features of the metabolism of erythrocytes

- as **RBC** lack cellular organelles, they are not capable of protein synthesis and repair.
- **RBC** have a life span of **~120** days.
- ~ **1%** or ≈ **30 trillion** erythrocytes replaced daily. This equates to a rate of production of ~ **2 million** new **RBC** per **second**.

Reticulocytes, retain the capacity to synthesize polypeptides under the direction of vestigial mRNA molecules.

Newly formed **RBC** during the ≈ 24 hours required to complete the transition to a **mature erythrocytes**.

Specific features of the metabolism of erythrocytes

- the **RBC** is highly dependent upon **glucose** as its energy source, for which its membrane contains high-affinity glucose transporters (**GLUT1**, **glucose permease**). It accounts for ~ **2%** of the protein of the membrane of the **RBC**.

  It is not dependent upon **insulin.**

- because **RBCs** lack mitochondria there is no production of **ATP** by oxidative phosphorylation. **Glycolysis**, producing **lactate**, is the mode of production of **ATP**.
- The **RBC** has a variety of **transporters** that maintain **ionic** and **water** balance.

Specific features of the metabolism of erythrocytes

- Production of **2,3-bisphosphoglycerate** by reactions closely associated with glycolysis is important in regulating the ability of **Hb** to transport O_2. (**Luebering-Rapoport pathway**)
- The **PPP** of the **RBC** metabolizes about **5-10%** of the total flux of **glucose** and produces **NAD(P)H_2**

Reduced **glutathione** (**GSH**) is important in the metabolism of the **RBC**, in part to counteract the action of potentially toxic **peroxides**. The **RBC** can synthesize **GSH** and the **NAD(P)H_2** required to return oxidized **G-S-S-G** to the reduced state - **GSH**.

Hemolytic anemia due to a deficiency of the activity of **glucose-6-phosphate dehydrogenase** is common.

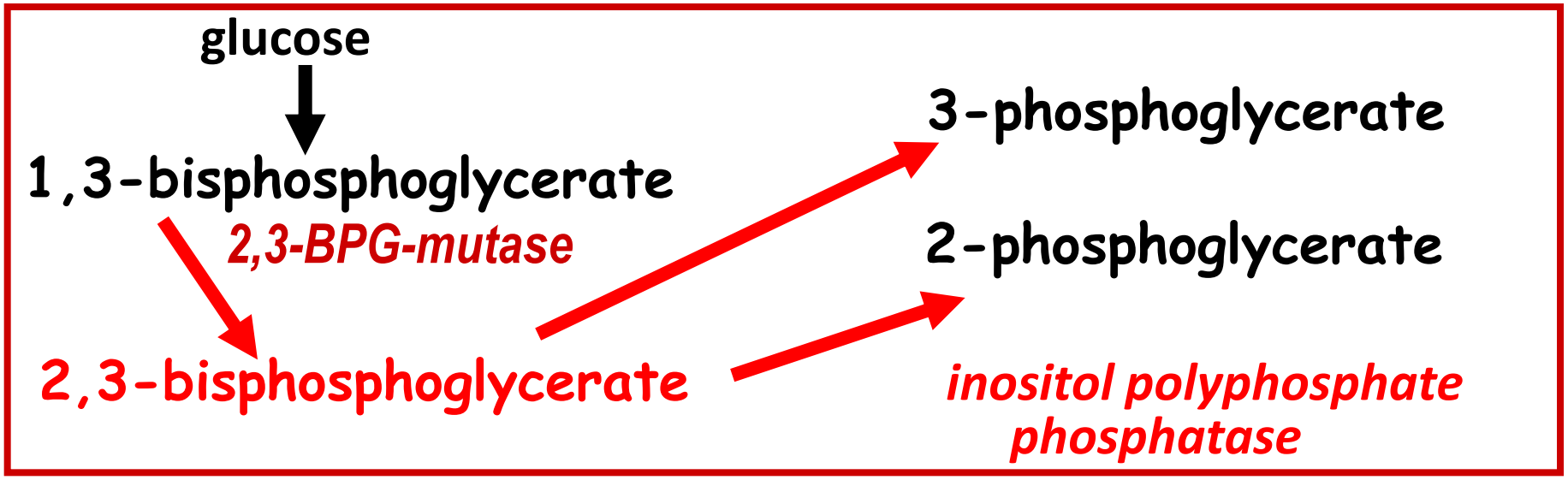
Specific features of the metabolism of erythrocytes

- **erythrocytes** also have systems that can inactivate **reactive oxygen species (ROS)** - **superoxide dismutase**, **catalase**, **GSH** - and protect **RBCs** from **oxidative stress** & **damage**.

- the reduction of **methemoglobin** (Hb **Fe^{3+}**) to **Hb** (Hb Fe^{2+}) is carried out by **GSH** or **ascorbate** by a non-enzymatic pathway – and **NAD(P)H**-dependent - **Met-Hb reductases**.

Luebering-Rapoport pathway.

Production of **2,3-bisphosphoglycerate** is important in **regulating** the ability of **Hb** to transport O_2.



The activities of these enzymes are sensitive to **pH**, which insures that **2,3-BPG** levels rise and fall at the appropriate times during the O_2 transport cycle.

- Bisphosphoglycerate (1,3-BPG) produced in glycolysis is converted to 2,3-BPG by the enzyme 2,3-bisphosphoglycerate mutase
- 2,3-BPG is hydrolysed to 3-phosphoglycerate by bisphosphoglycerate phosphatase.
- Bisphosphoglycerate mutase is a bifunctional enzyme with mutase & phosphatase activities.
- About 15-25% of the glucose that gets converted to lactate in erythrocytes goes via 2,3-BPG synthesis.

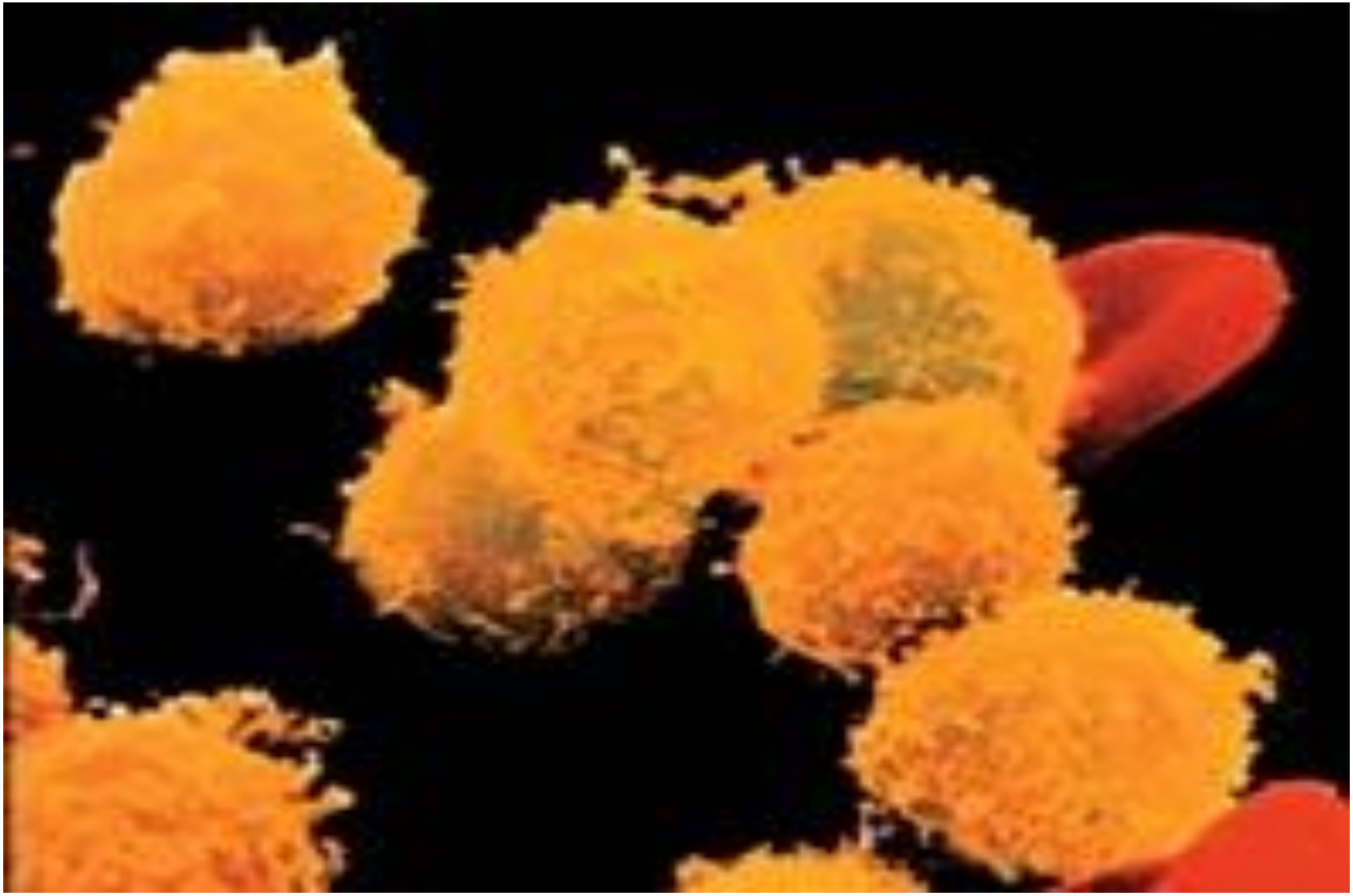
Significance of 2,3-BPG

- The 2,3-BPG combines with hemoglobin & reduces the affinity towards oxygen.
- In presence of 2,3-BPG, oxyhemoglobin will unload oxygen more easily in tissues.
- Under hypoxic conditions the 2,3-BPG concentration in the RBC increases, thus favoring the release of oxygen to the tissues even when PO_2 is low.

Specific features of the metabolism of erythrocytes

- While biosynthesis of **glycogen**, **fatty acids**, **protein**, and **nucleic acids** does not occur in the **RBC**, some lipids (eg, **cholesterol**) in the red cell membrane can exchange with corresponding **plasma lipids**.
- The **RBC** contains certain enzymes of nucleotide metabolism (eg, ***adenosine deaminase***, ***pyrimidine nucleotidase***, and ***adenylyl kinase***). Deficiencies of these enzymes are involved in some cases of **hemolytic anemia**.
- When **RBCs** reach the end of their lifespan, the **globin** is degraded to amino acids, the **iron** is released from heme and reutilized, and the **tetrapyrrole** component of **heme** is converted to **bilirubin**, which is mainly excreted into the bowel via the **bile**.

Leukocytes



The immune system can be classified as

- the **innate immune system**
- the **adaptive immune system**.

The **innate immune system** defends against infection in a **nonspecific manner**.

Leukocytes are the second arm of the innate immune system.
The innate leukocytes include:

- the **phagocytes** (macrophages, neutrophils, and dendritic cells),
- **innate lymphoid cells**,
- **mast cells**,
- **eosinophils**,
- **basophils**, and
- **natural killer cells** - does not directly attack invading microbes. NK cells destroy compromised host cells, such as tumor cells or virus-infected cells.

These cells identify and eliminate pathogens.

Innate cells are also important mediators in lymphoid organ development and the activation of the **adaptive immune system**.

The cells of the **adaptive immune system** are special types of leukocytes, called **lymphocytes**.

B cells and **T cells** are the major types of **lymphocytes** and are derived from hematopoietic stem cells in the bone marrow.

- **B cells** are involved in the **humoral** immune response,
- **T cells** are involved in **cell-mediated** immune response.

There are two major subtypes of **T cells**:

- the **killer T cell** and
- the **helper T cell**.
- In addition there are **regulatory T cells** which have a role in **modulating** immune response.

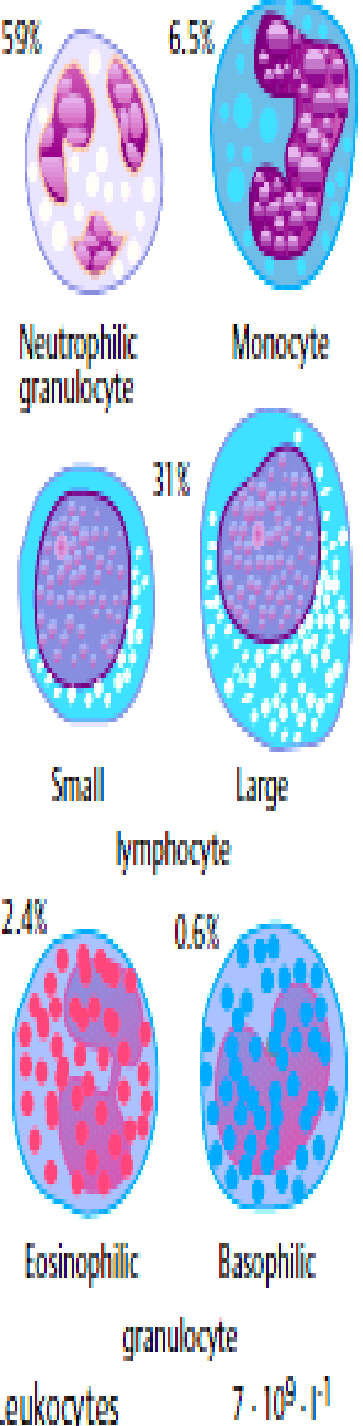
Both **B cells** and **T cells** carry **receptor** molecules that recognize specific targets.

The **T cells** are exposed to a wide variety of self-antigens in the **thymus**, in which **iodine** is **necessary** for its thymus development and activity.

The **B cells** are responsible for the synthesis of circulating, humoral **antibodies**, also known as **immunoglobulins**.

The **T cells** are involved in a variety of important **cell mediated immunologic processes** such as

- **graft rejection**,
- **hypersensitivity reactions**, and
- **defense** against **malignant cells** and many **viruses**.



Leukocytes

include various types of **granulocyte**, **monocyte**, and **lymphocyte**.

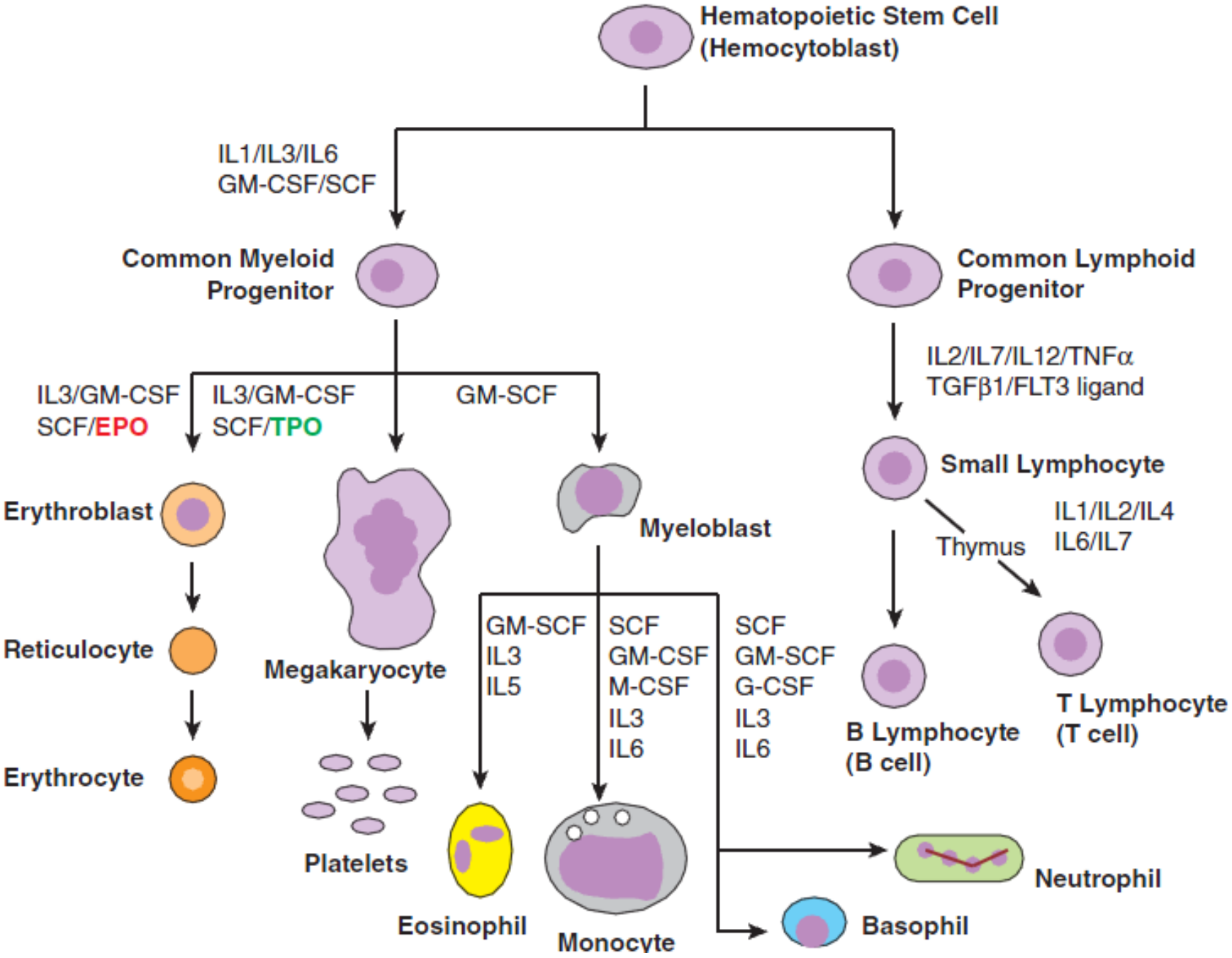
All of these have **immune defense functions.**

- The ***neutrophil granulocytes, monocytes,*** and the ***macrophages*** can ingest and degrade pathogens**.**
- ***Eosinophilic*** and ***basophilic granulocytes*** have special tasks for defense against animal **parasites**.

- The ***lymphocytes*** are divided into two groups:

• **B lymphocytes** produce ***antibodies,***

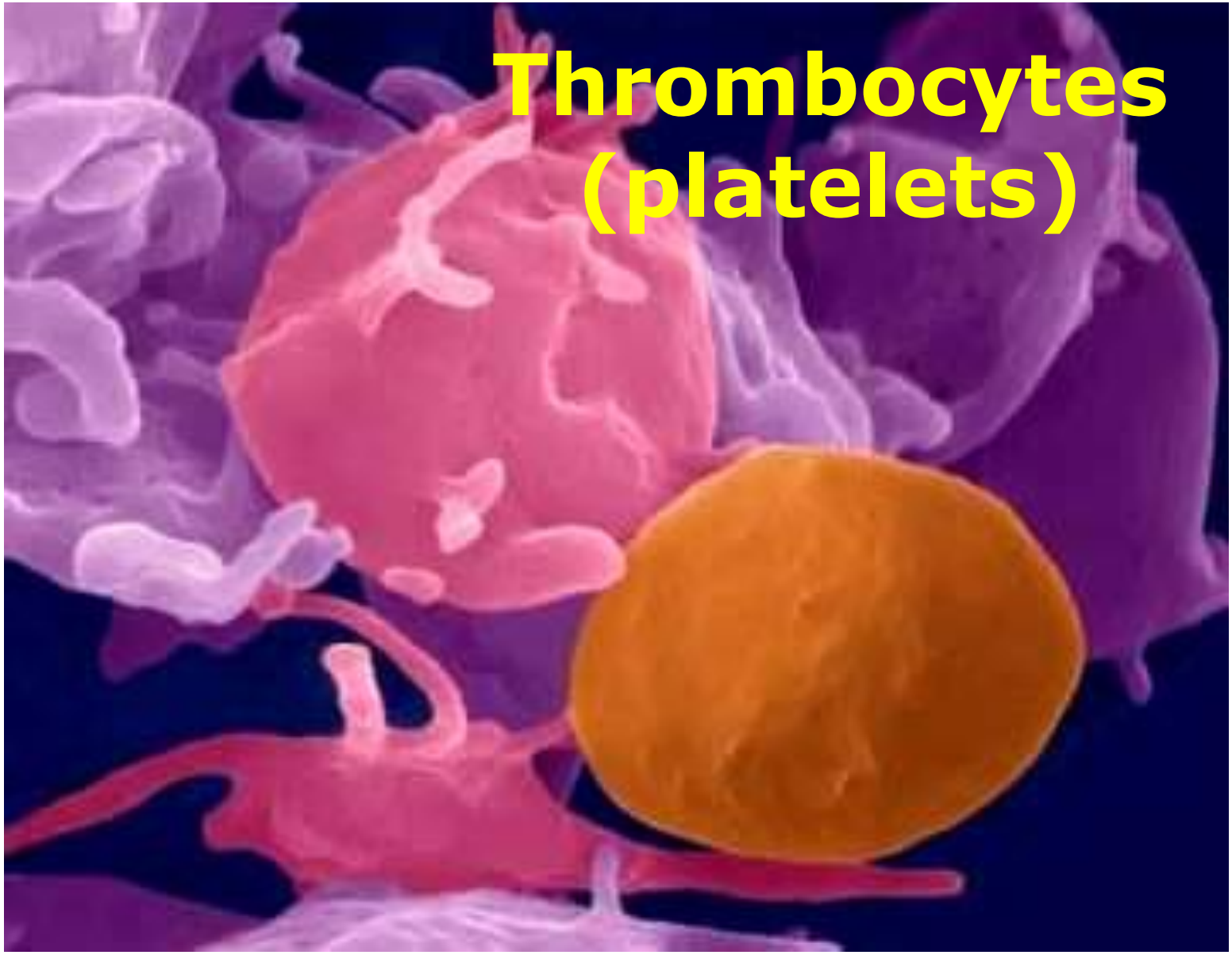
• **T lymphocytes regulate** the immune response and **destroy** virus infected cells and tumor cells.


Hematopoietic Stem Cell
(Hemocytoblast)
IL1/IL3/IL6
GM-CSF/SCF
Common Myeloid
Progenitor
Common Lymphoid
Progenitor
IL2/IL7/IL12/TNFα
TGFβ1/FLT3 ligand
IL3/GM-CSF
SCF/EPO
IL3/GM-CSF
SCF/TPO
GM-SCF
Small Lymphocyte
IL1/IL2/IL4
IL6/IL7
Thymus
Erythroblast
Myeloblast
Reticulocyte
Megakaryocyte
GM-SCF
IL3
IL5
SCF
GM-CSF
M-CSF
IL3
IL6
SCF
GM-SCF
G-CSF
IL3
IL6
B Lymphocyte
(B cell)
T Lymphocyte
(T cell)
Erythrocyte
Platelets
Eosinophil
Monocyte
Neutrophil
Basophil

In order to function correctly, **leukocytes** have the ability to **migrate** out of the bloodstream into surrounding tissues.

Major biochemical features of leukocytes

1. active **synthesis** of **proteins** and **nucleic acids**;
2. synthesis and storage of **glycogene**;
3. active **glycolysis**;
4. moderate **oxidative phosphorylation**;
5. active **pentose phosphate pathway**;
6. rich in **lysosomes** and their degradative enzymes;
7. contain certain unique enzymes - **myeloperoxidase**, **Nox – NADPH oxidase**)
8. can exhibit a rapid increase of O_2 consumption and production of **ROS** which are potent **microbicidal agents - respiratory burst -**


Thrombocytes
(platelets)

Thrombocytes (platelets)

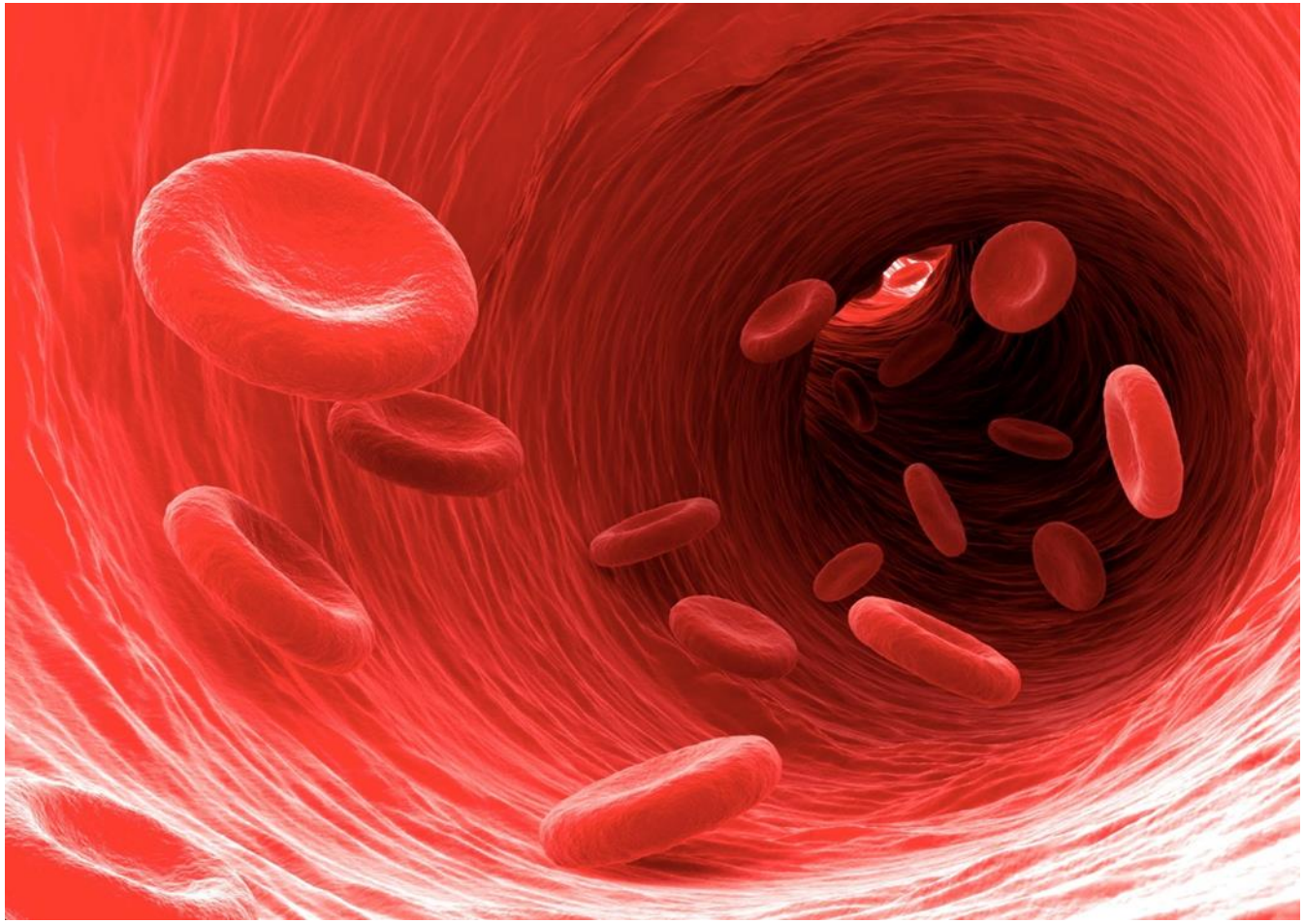
In response to **thrombopoietin**, the **megakaryocytes** can fragment to form **platelets**.

Like RBC, **platelets** lack a nucleus, but unlike RBC they possess **mitochondria**, **lysozymes**, and a **tubular network** that forms an open **canalicular system**.

This channels increases the surface area of the **platelets** facilitating the secretion of various **endocrine** and **coagulation factors** upon stimulation.

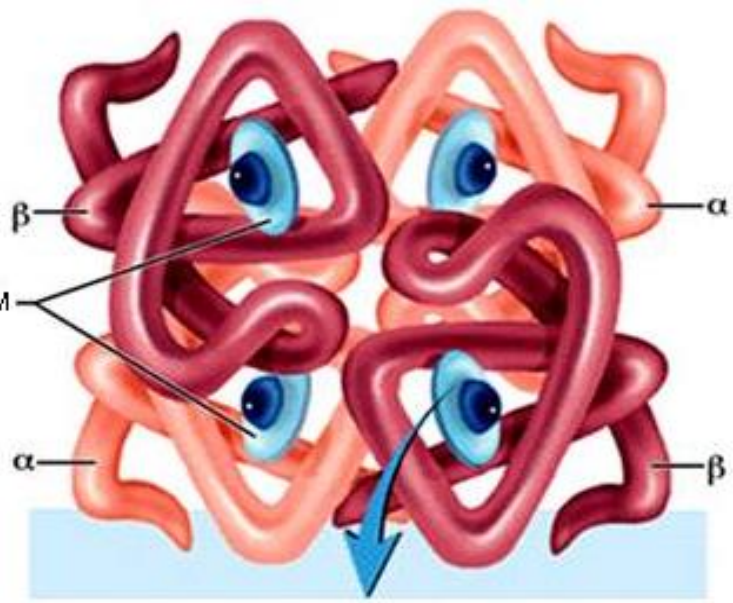
These factors are stored inside the platelets within densely packed secretory vesicles, called

- **dense granules**, which contain **Ca^{2+}**, **ADP** and **serotonin**, and
- **α-granules**, which contain **fibrinogen**, **fibronectin**, **platelet derived growth factor**, **von Willebrand factor**, other coagulation factors.



Red blood cells

Hemoglobin



Human hemoglobin

In adults, **Hb** is a heterotetramer consisting of two α-globin and two β-globin subunits:

α2β2

Each subunit carries a **heme group**, with a central bivalent **iron** ion.

Hemoglobin can bind up to four molecules of O_2.

Hemoglobin derivatives

Deoxyhemoglobin (HHb) not combined with O_2, formed when oxyhemoglobin releases its O_2 to the tissues.

Oxyhemoglobin ($HHbO_2$) the oxygen-carrying **Hb**.

Carbhemoglobin ($HHbCO_2$) is compound of **Hb** and carbon dioxide, is one of the forms in which CO_2 exists in the blood.

Carboxyhemoglobin (**COHb**) is a stable complex of carbon monoxide and **Hb** that forms in red blood cells upon contact with carbon monoxide (**CO**).

Methemoglobin (**MetHb**) is a form of **Hb**, in which the iron in the heme group is in the Fe^{3+} state. **MetHb** cannot bind O_2.

Variants of hemoglobin in ontogenesis

- **Embryonic hemoglobins** - **α2ε2** - globin chain are formed in the first three months of embryonic development.
- **Fetal Hb (HbF)** - **α2γ2** - predominates in the fetus during the second and third trimesters of gestation and in the neonate. The most striking functional difference between **HbF** and **HbA** is its decreased sensitivity to **2,3-bisphosphoglycerate.**

***Embryonic** and **fetal hemoglobins** have higher O_2 affinities than **HbA**, as they have to take up O_2 from the maternal circulation.*

- **HbF** is gradually replaced by **HbA** **during the first few months of life. Over 95% of the Hb found in adult humans is HbA**
- **HbA_2** accounts for **2-3%** of the total and has an **α2δ2** polypeptide composition. **HbA_2** is elevated in **β-thalassemia,** a disease characterized by a deficiency in **β-globin** biosynthesis. Functionally, these two adult **Hbs** are indistinguishable.

Hemoglobinopathies

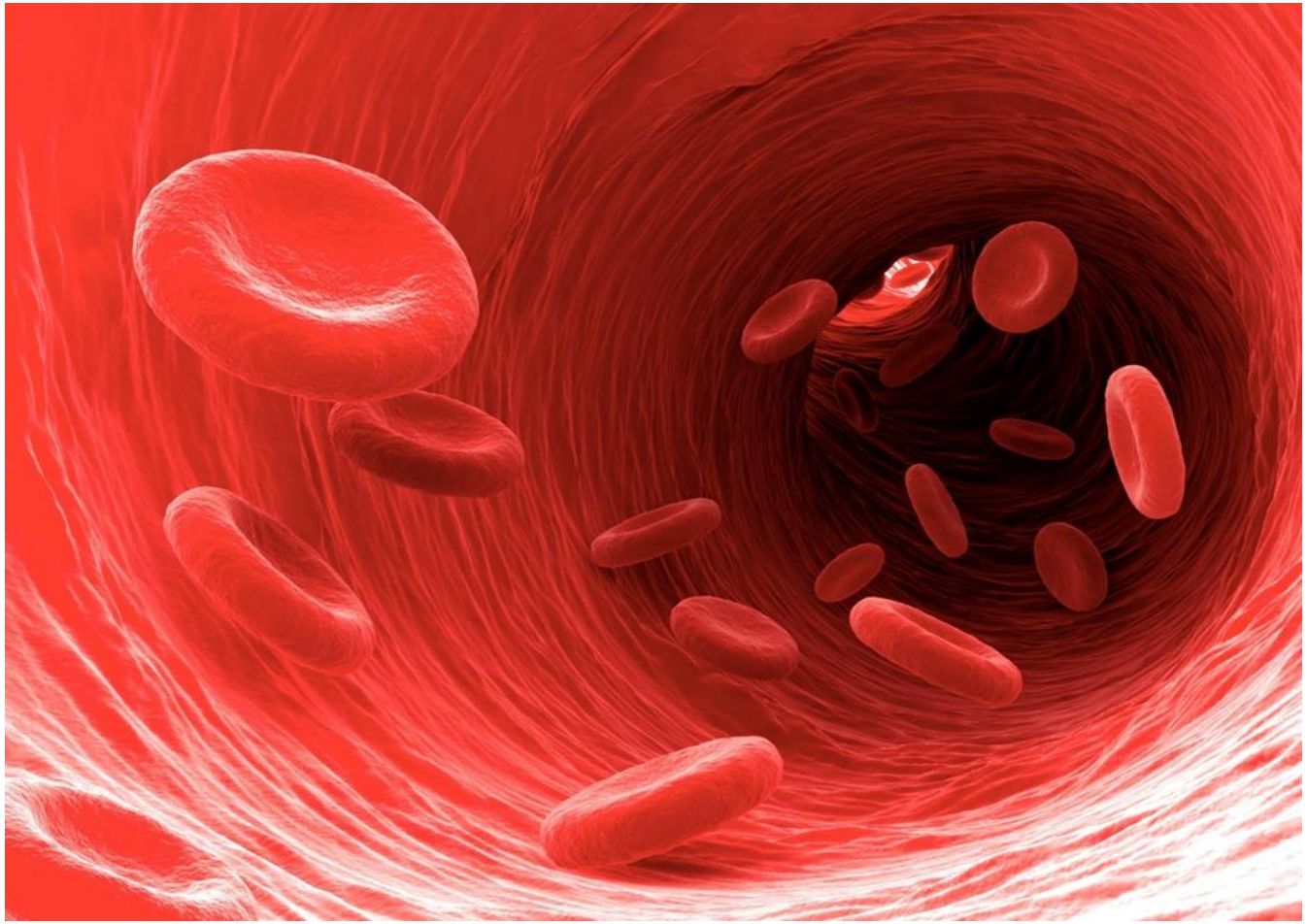
- inherited single-gene disorders that results in abnormal structure of one of the globin chains of the hemoglobin molecule.

Hemoglobinopathies are classified according to the type of structural change and altered function and the resulting clinical characteristics.

Common **hemoglobinopathies** include

sickle-cell disease.

Many **hemoglobin** variants do not cause pathology or anemia, and thus are often not classed as **hemoglobinopathies**, because they are not considered pathologies.



Iron metabolism

Iron metabolism

The human body contains **4-5g iron**, which is almost exclusively present in protein-bound form.

- Approximately three-quarters of the total amount is found in **hemoproteins**, mainly **hemoglobin** and **myoglobin.**
- About **1%** of the **iron** is bound in **iron-sulfur clusters**, which function as cofactors in the respiratory chain, and in other redox chains.
- The remainder consists of **iron** in transport and storage proteins.

Iron metabolism

Absorption of nonheme **iron** by enterocytes of the proximal duodenum is a highly regulated process.

Inorganic dietary **iron** in the **ferric** state (**Fe^{3+}**) is reduced to its **ferrous** form (**Fe^{2+}**) by a brush border membrane-bound ***ferrireductase*** - **duodenal cytochrome b (Dcytb)**.

Vitamin C, **gastric acid**, and a number of other reducing agents present in food may also favor reduction of **ferric** to **ferrous** iron.

The transfer of **iron** across the apical membrane of the enterocytes is accomplished via the **divalent metal transporter1** (**DMT1**)

Iron metabolism

Inside the **enterocytes**, **iron** can either be stored bound to the **iron** storage protein - **ferritin** - or transferred across the basolateral membrane into the circulation by the **iron** exporter protein - **ferroportin** or **iron-regulated protein 1** (**IREG1**).

Iron is stored intracellularly by **ferritin**, a major iron storage protein complex composed of **24 heavy** (**FtH**) chains and **24 light** (**FtL**) chains, can bind up to **4,500** $\mathbf{Fe^{3+}}$ ions.

Any excess ferritin-bound **iron** retained by the **enterocytes** is disposed of when the **enterocytes** are sloughed off into the gut lumen.

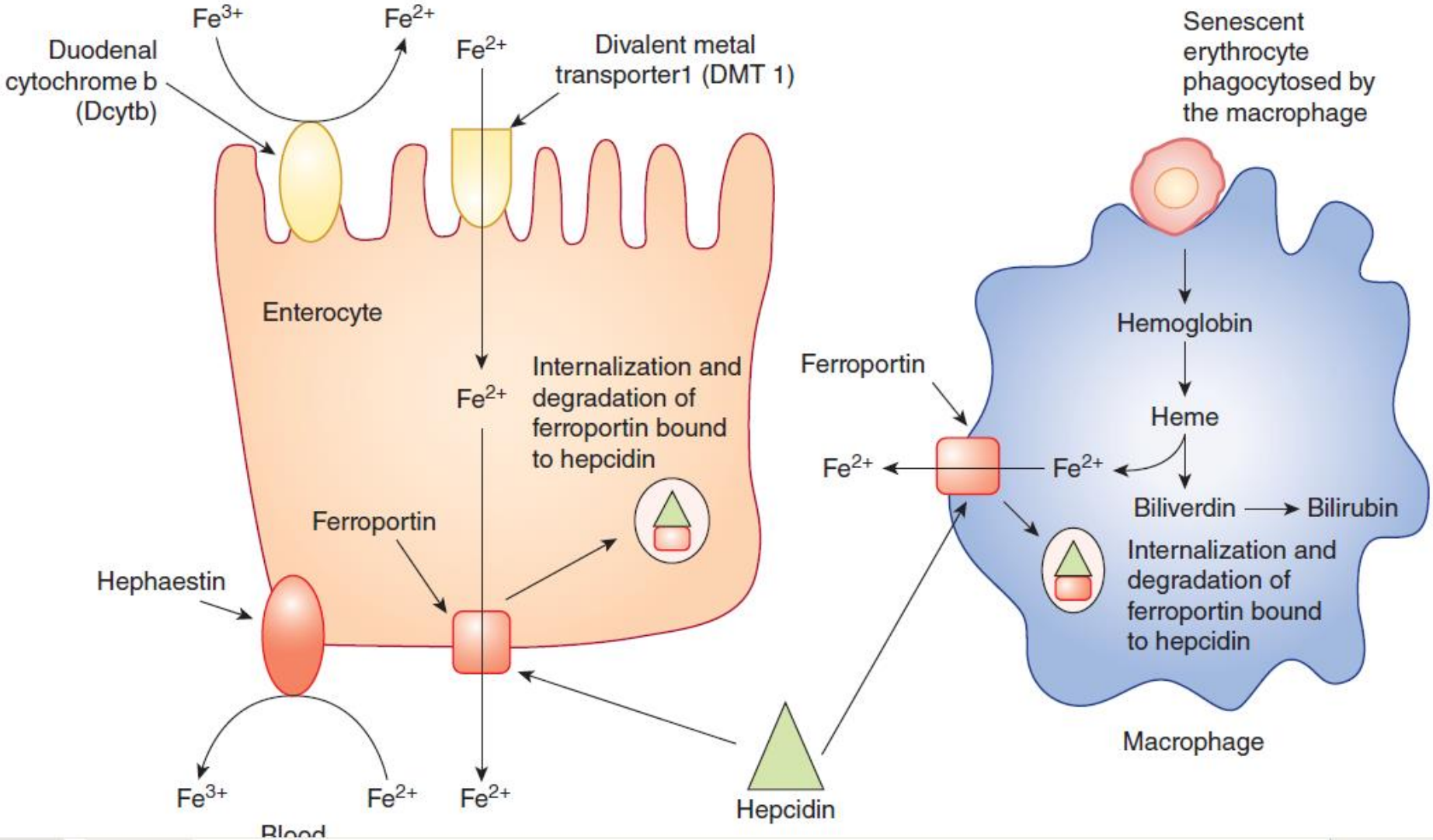
Iron metabolism

Hephaestin, a copper-containing **ferroxidase**, oxidizes **Fe^{2+}** to **Fe^{3+}** prior to export.

Iron is transported in plasma in the **Fe^{3+}** form by the transport protein - **transferrin**.

The 25-amino acid peptide **hepcidin** plays a central role in iron homeostasis.

Synthesized in the liver, **hepcidin** binds to the cellular **iron** exporter, **ferroportin**, triggering its internalization and degradation. The consequent decrease in **ferroportin** results in decreased iron absorption in the intestine (producing a "**mucosal block**")



Hepcidin synthesis is induced by **cytokines** such as **interleukin-6 (IL-6)** that are released as part of an inflammatory response. Binding of **IL-6** to its cell surface **receptor** stimulates **hepcidin** gene expression.

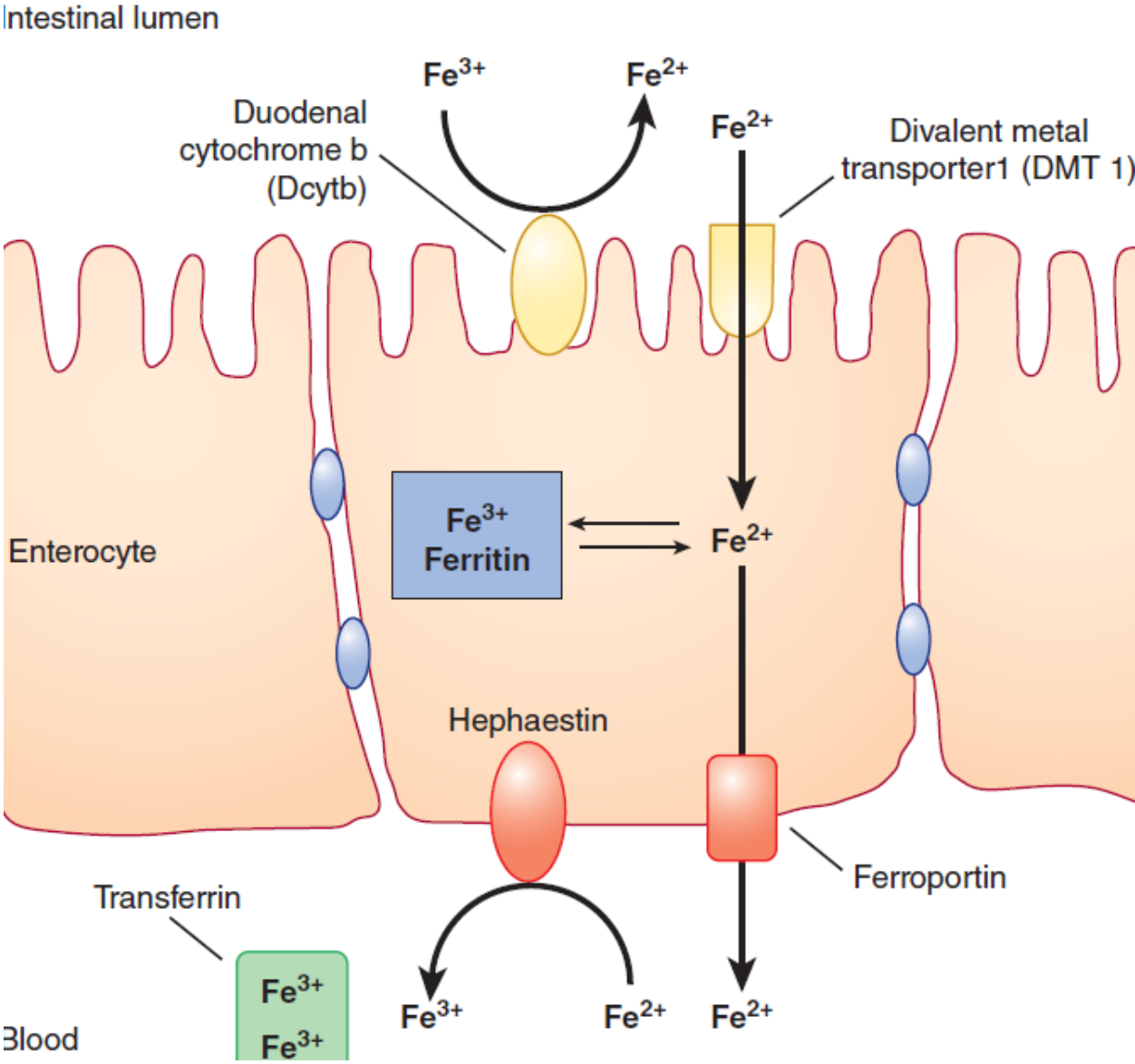
Anemia that is associated with chronic inflammation - **anemia of inflammation** (**AI**) - is due to inflammation mediated **upregulation** of **hepcidin**. **AI** manifests as a microcytic, hypochromic anemia that **is refractory to iron supplementation**.

Hypoxia is suppress **hepcidin** expression. This effect is mediated by **erythropoietin**, whose synthesis is controlled by **hypoxia-inducible transcription factors 1** and **2** (**HIF-1, HIF-2**)

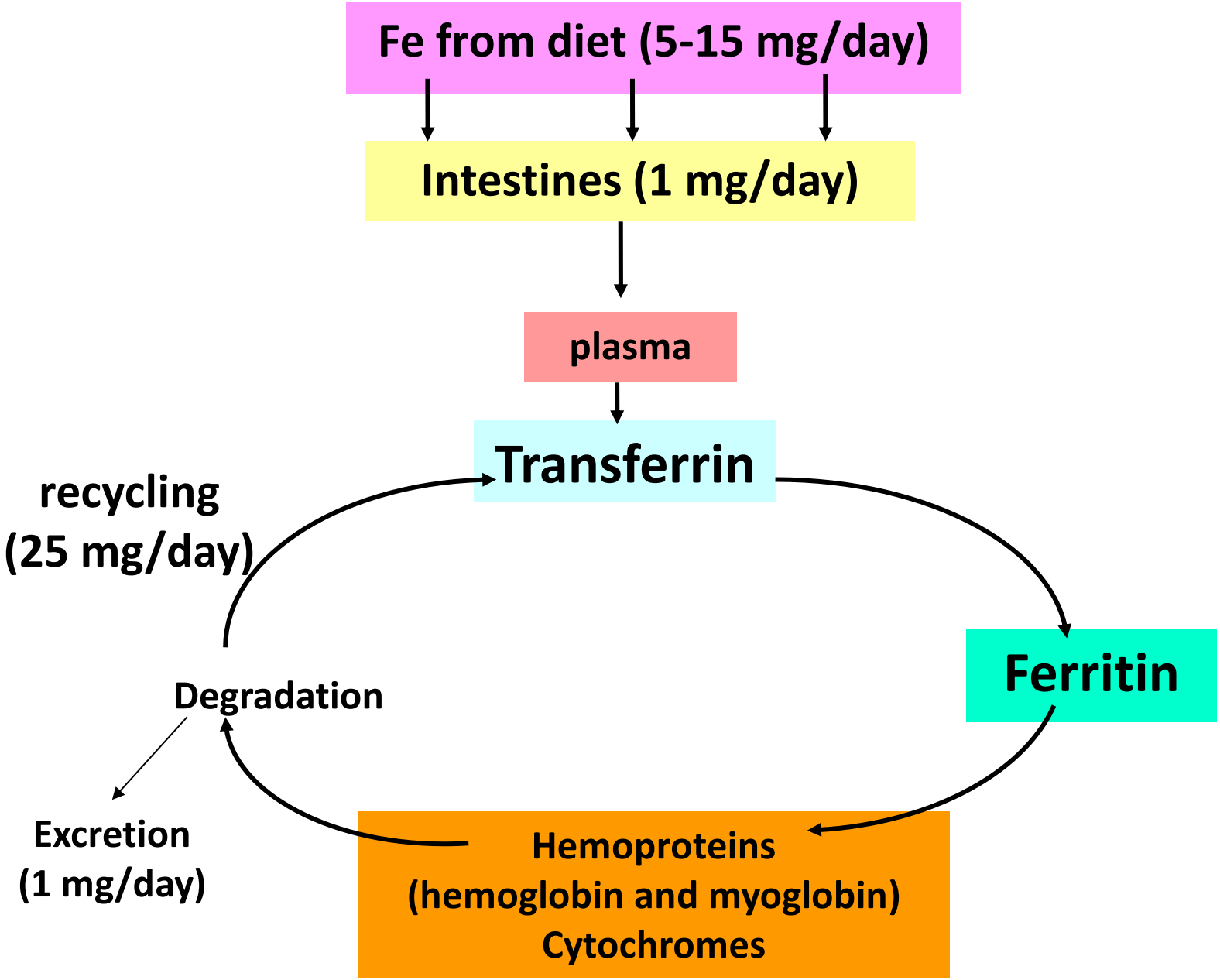
Ferric iron is reduced to the **Fe^{3+}** by a luminal, **duodenal cytochrome b.**

Fe^{3+} is transported into the enterocyte via **divalent metal transporter-1**.

Within the enterocyte, **iron** is either stored as **ferritin**, or transported out of the cell by **ferroportin**.



Fe^{2+} is oxidized to its **Fe^{3+}** by **hephaestin**. The **ferric iron** is then bound by **transferrin** for transport by the blood to various sites in the body.


Fe from diet (5-15 mg/day)
Intestines (1 mg/day)
plasma
Transferrin
recycling
(25 mg/day)
Ferritin
Degradation
Excretion
(1 mg/day)
Hemoproteins
(hemoglobin and myoglobin)
Cytochromes

Iron metabolism

- Most of the resorbed **iron** serves for the formation of **RBC** in the **bone marrow**. In the blood, **2.5–3.0 g** of **Hb iron** circulates as a component of the **erythrocytes**. After the heme degradation the **iron** returns to the plasma pool.

- Excess **iron** is incorporated into **ferritin** and stored in this form in the liver and other organs. Each **ferritin** molecule is capable of storing several thousand **iron** ions.

- **Hemosiderin** is an **iron**-storage complex. It is only found within cells and appears to be a complex of **ferritin**, denatured **ferritin** and other material. The **iron** within deposits of **hemosiderin** is very poorly available to supply **iron** when needed. Excessive accumulation of **hemosiderin** is usually detected within cells of the **mononuclear phagocyte system** (MPS) or occasionally within **epithelial cells** of **liver** and **kidney**.

Iron-deficiency anemias

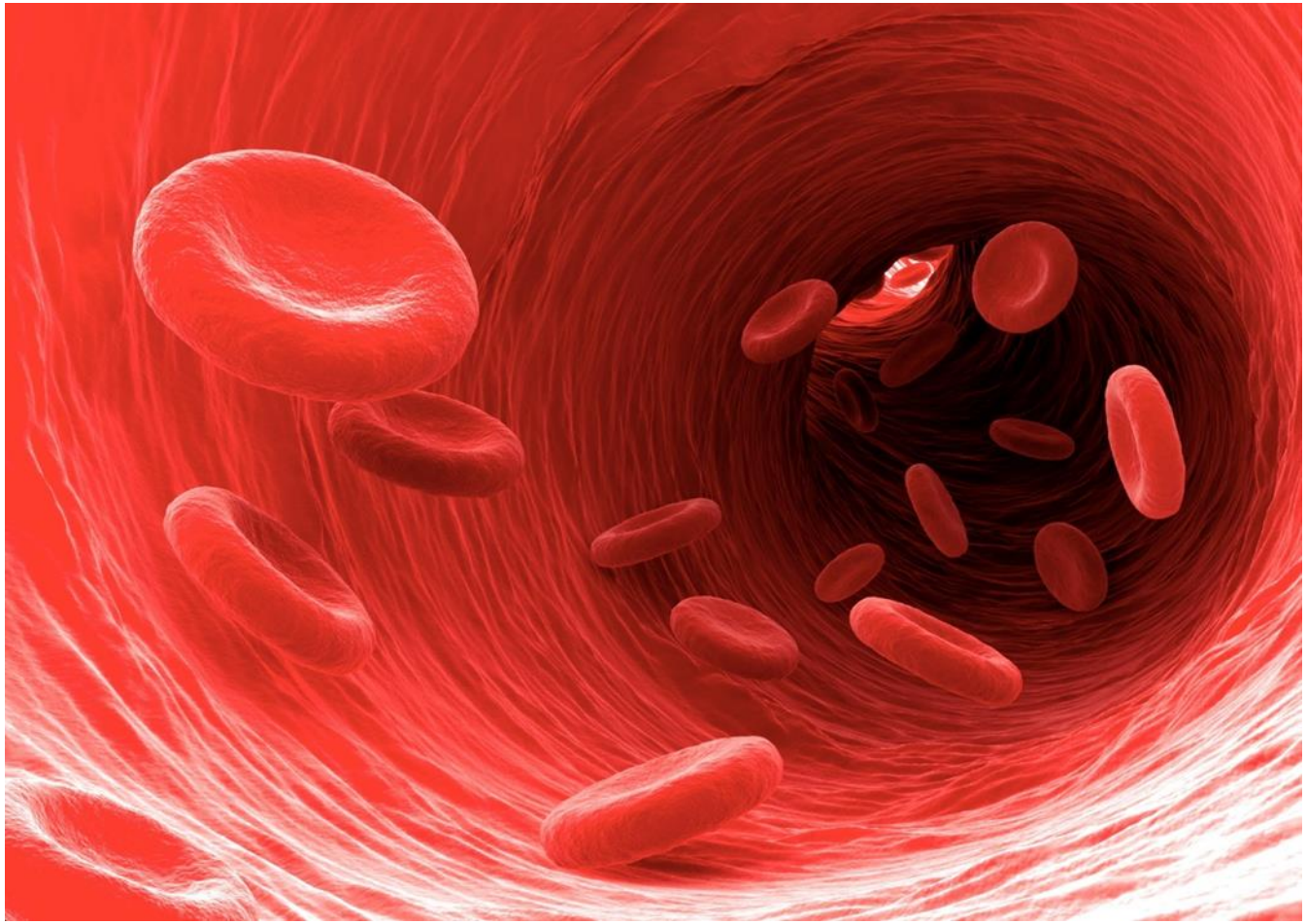
Iron deficiency is usually due to **blood** loss, or more rarely to inadequate **iron** uptake.

During **pregnancy**, increased demand can also cause **iron** deficiency states.

In severe cases, reduced **hemoglobin** synthesis can lead to anemia **- "iron-deficiency anemia"**. In these patients, the erythrocytes are smaller and have less **Hb**.

Iron-deficiency anemias

WHO defines anemia
as a hemoglobin level
of < **130 g/L** in men
and < **120 g/L** in females



Plasma proteins

Plasma proteins

Plasma contains many proteins broadly classified into

- **albumin** and
- **globulins** (predominantly **immunoglobulins**).

Albumin is a:

- major **transport protein** - **trace metals**, **hormones**, **bilirubin**, and **free fatty acids**;
- **protein reserve** in nutritional depletion;
- **osmotic regulator**.

Albumin accounts for ~ **50%** of the protein found in human plasma at a concentration of **35-45 g/L**.

Other proteins are more specialized: **ceruloplasmin** binds **Cu^{2+}**, and **thyroid binding globulin** binds thyroid hormones.

Plasma proteins

Immunoglobulins are molecules that participate in the defense against antigens.

They have a common structure and **five classes** of immunoglobulin exist with different protective functions. **Immunoglobulins** are produced in response to foreign substances (**antigens**).

Acute phase proteins

The acute phase response is a nonspecific response to tissue injury or infection; it affects several organs and tissues.

Acute phase response is a characteristic pattern of change in certain proteins along with a decrease in the plasma concentration of some others.

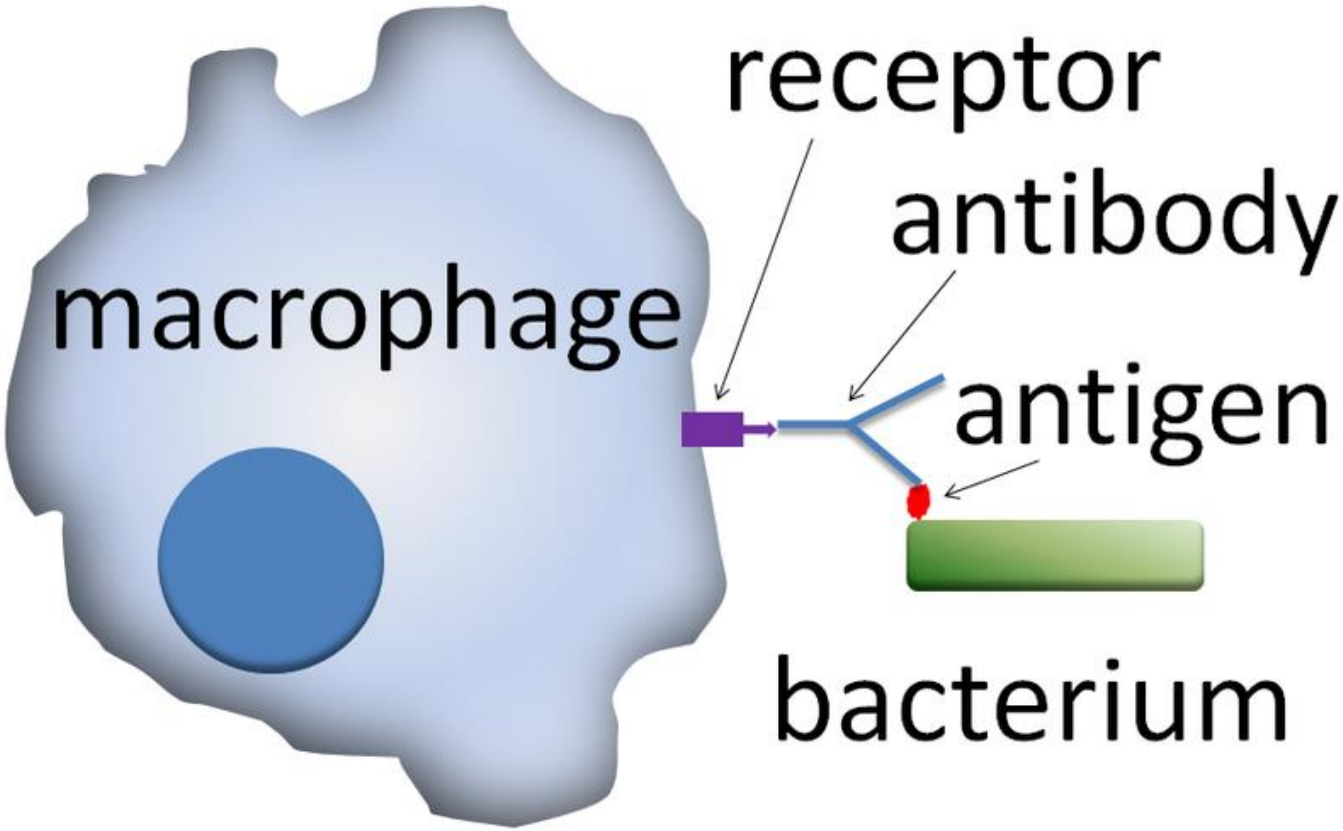
- An increase in the synthesis of proteins such as
  - proteinase inhibitors - α1-antitrypsin,
  - coagulation proteins - fibrinogen, prothrombin,
  - complement proteins,
  - C-reactive protein, etc.

Acute phase proteins

The production of these proteins have a central role in the induction of the **acute phase response**.

The **acute phase proteins** have a number of different functions in the response to inflammation:

- **binding proteins**, **opsonins**, **C-reactive protein (CRP)**, bind to macromolecules released by damaged tissue or infective agents and promote their phagocytosis.
- **complement factors** promote the phagocytosis of foreign molecules.
- **protease inhibitors**, such as **α1-antitrypsin** and **α1-antichymotrypsin** inhibit proteolytic enzymes.



Action of **opsonins**: a phagocytic cell recognises the **opsonin** on the surface of an antigen.

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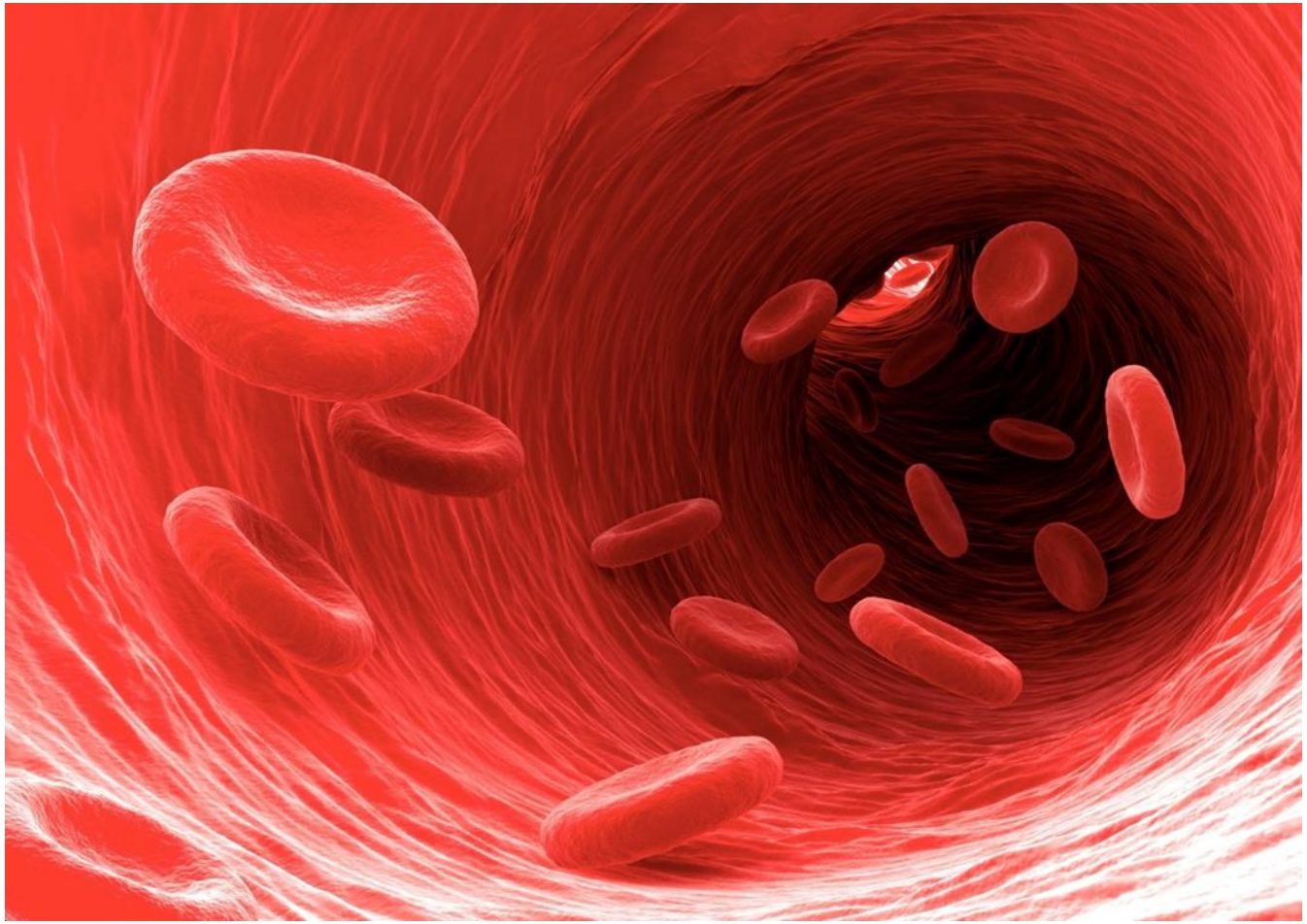


Hemostasis & Thrombosis

Hemostasis & Thrombosis

Hemostasis is the cessation of bleeding from a cut or severed vessel, whereas thrombosis occurs when the endothelium lining blood vessels is damaged or removed.

Hemostasis & Thrombosis

In **hemostasis**, there is initial **vasoconstriction** of the injured vessel, causing diminished blood flow distal to the injury. Then, **hemostasis** and **thrombosis** share **three phases**:

1. **Formation of platelet aggregate** at the site of injury.
   Platelets bind to **collagen**, form **thromboxane A_2**, and release **ADP**, which activate other platelets flowing by the vicinity of the injury. **Thrombin**, formed during coagulation at the same site, causes further **platelet activation**. Upon activation, **platelets** change shape and, in the presence of **fibrinogen** and **von Willebrand factor**, aggregate to form the **hemostatic plug** (in **hemostasis**) or **thrombus** (in **thrombosis**).

Hemostasis & Thrombosis

2. Formation of a **fibrin mesh** that binds to the **platelet aggregate**, forming a more stable **hemostatic plug** or **thrombus**.

3. Partial or complete dissolution of the **hemostatic plug** or **thrombus** by **plasmin**.

Hemostasis & Thrombosis

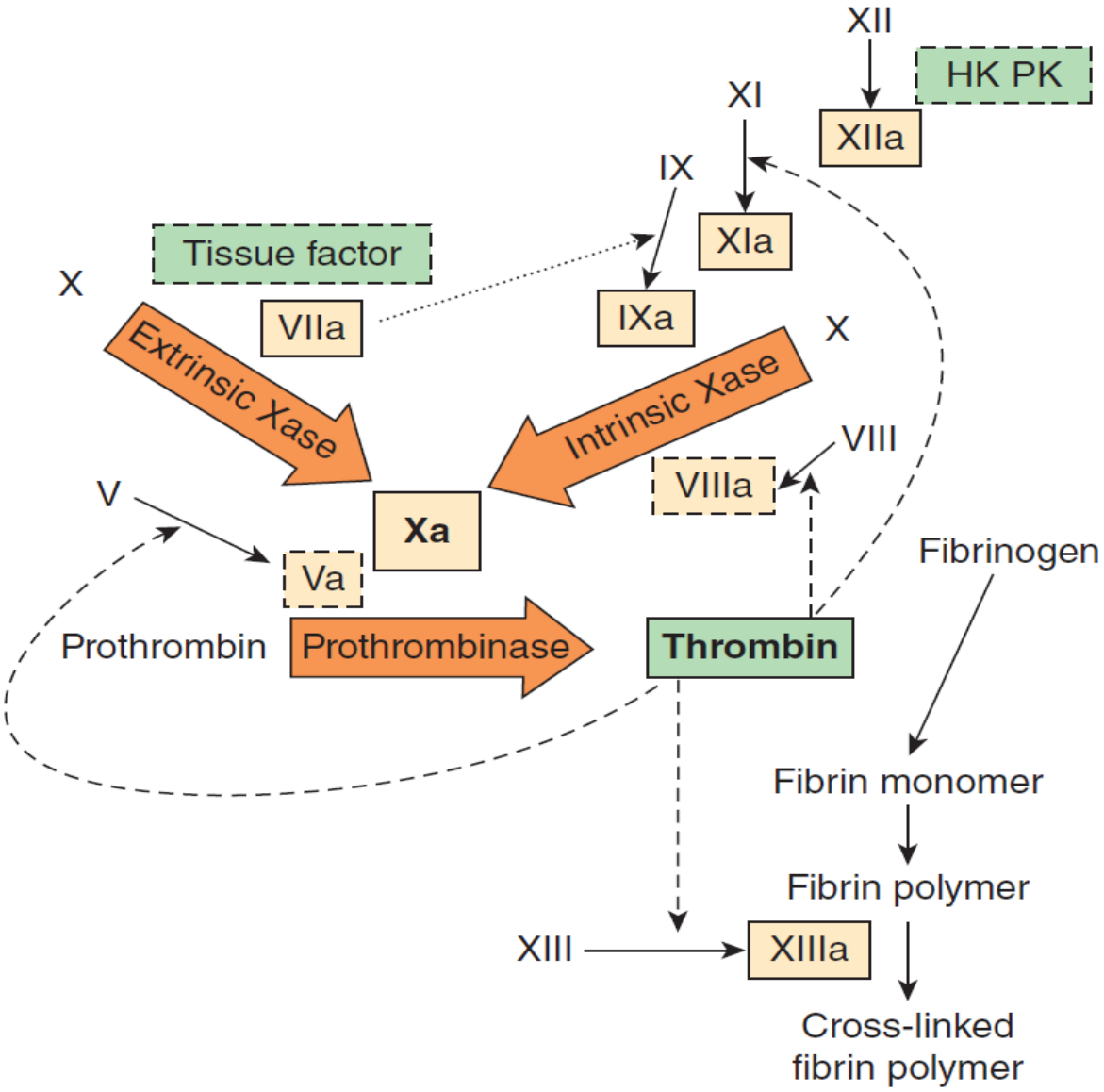
Three types of **thrombi** or **clots**:

1. The **white thrombus** is composed of **platelets** and **fibrin** and is relatively poor in **erythrocytes**.
2. The **red thrombus** consists primarily of **red cells** and **fibrin**.
3. **Fibrin** deposits in very small blood vessels or capillaries.

Fibrin is derived from circulating **fibrinogen**. During clotting, **fibrinogen** is converted to fibrin as a result of proteolytic cleavage by **thrombin**.

Prothrombin is activated in two ways: **intrinsic** and **extrinsic.**

Hemostasis & Thrombosis



HK - high-molecular-weight kininogen;

PK - prekallikrein

Hemostasis & Thrombosis

Factor	Common Name
I	Fibrinogen
II	Prothrombin
III	Tissue factor
IV	Ca^{2+}
V	Proaccelerin
VII	Proconvertin
VIII	Antihemophilic factor **A**,
IX	Antihemophilic factor **B**, Christmas factor.
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hageman factor
XIII	Fibrin stabilizing factor (FSF)

Regulation of **blood clotting**

To prevent the coagulation reaction from becoming excessive, the blood contains a number of **anticoagulant substances**, including proteinase inhibitors:

- **antithrombin III** binds to various proteinases in the cascade and thereby inactivates them.
- **Heparin**, an anticoagulant, potentiates the effect of antithrombin III.
- **Thrombomodulin**, which is located on the vascular endothelia, also inactivates thrombin.

Regulation of **blood clotting**

The **coumarin drugs** (eg, **warfarin**), which are used as anticoagulants, inhibit the **vitamin K**–dependent carboxylation of Glu to **gamma-carboxyglutamate** (**Gla**) residues in the amino terminal regions of factors **II**, **VII**, **IX**, and **X** and also **proteins C** and **S**.

These proteins, all of which are synthesized in the **liver**, are dependent on the Ca^{2+}-binding properties of the **Gla** residues for their normal function in the coagulation pathways.

Fibrinolysis

- The **fibrin thrombus** resulting from blood clotting is dissolved again by **plasmin**, a proteinase found in the blood plasma. For this purpose, the precursor **plasminogen** first has to be proteolytically activated by enzymes from various tissues.
- This group includes the **plasminogen activator** from the kidney (**urokinase**) and **tissue plasminogen activator** (t-PA) from vascular endothelia.

By contrast, the plasma protein **antiplasmin**, which binds to active **plasmin** and thereby inactivates it, inhibits fibrinolysis.

Urokinase, **t-PA**, and **streptokinase** - a bacterial proteinase with similar activity - are used clinically to dissolve **thromb** following **heart attacks**.

Hemophilias

a group of genetic disorders that impair the body's ability to control blood clotting.

- **Hemophilia A** (factor VIII deficiency) is the most common form of the disorder.
- **Hemophilia B** (factor IX deficiency) occurs rarely.

Like most recessive sex-linked,

X chromosome disorders, **hemophilia** is more likely to occur in males than females.

Disseminated intravascular coagulation

- is a pathological activation of coagulation mechanisms.

DIC leads to the formation of small blood **clots** inside the blood vessels throughout the body.

As the **small clots** consume coagulation proteins and platelets, normal coagulation is disrupted and abnormal bleeding occurs from the skin, the GIT, the respiratory tract and surgical wounds.

The **small clots** also disrupt normal blood flow to organs (such as the kidneys), which may malfunction as a result.

DIC can occur acutely but also on a slower, chronic basis.