

Pathophysiology of hematopoietic system I– hematological malignancies

Assoc. Prof. RNDr. Sabina Ševčíková, PhD.
Babak Myeloma Group
Department of Pathophysiology

M U N I
M E D

I. Hematopoiesis

Hematopoiesis



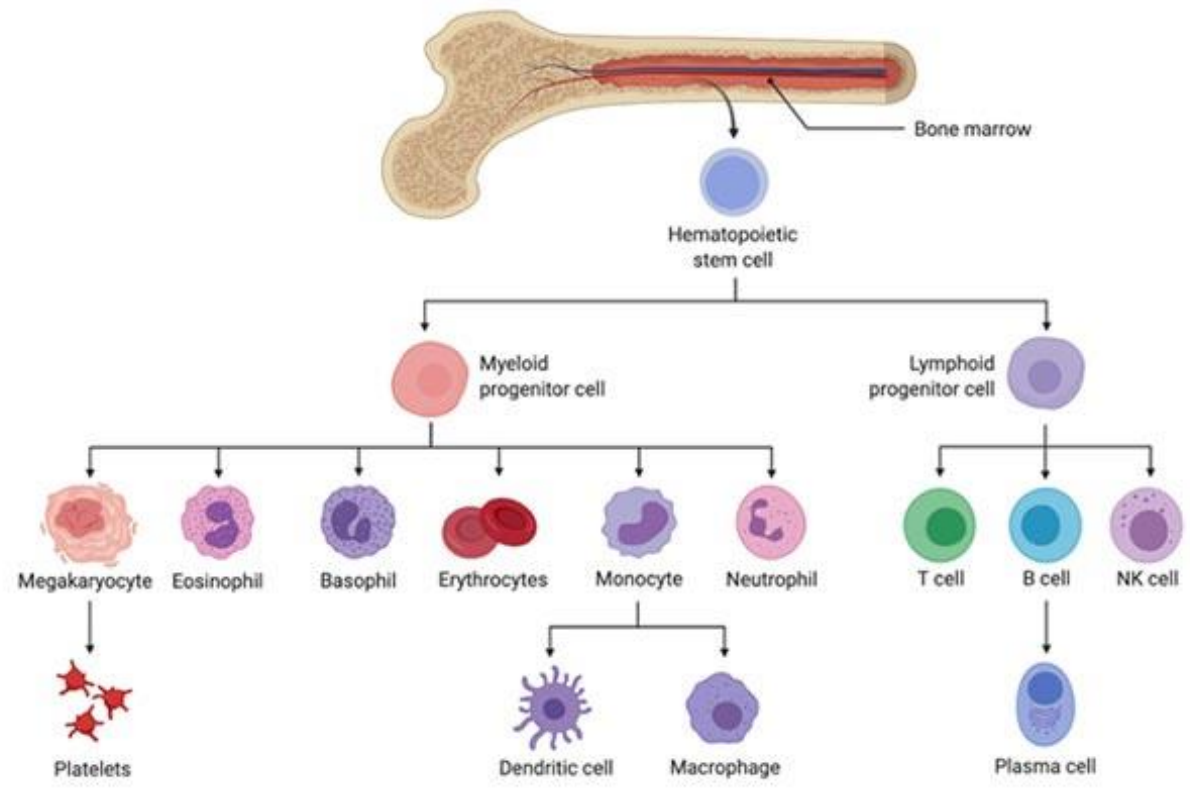
process of creation of cell components of blood



adult human produces $4 - 5 \times 10^{11}$ of hematopoietic cells daily



highly regulated, highly responsive system



Production and destruction of blood

- **Production of blood**

- the liver creates protein components of blood
- the endocrine glands produce hormones
- the GI tract and kidneys maintain water fraction

- **Destruction of blood**

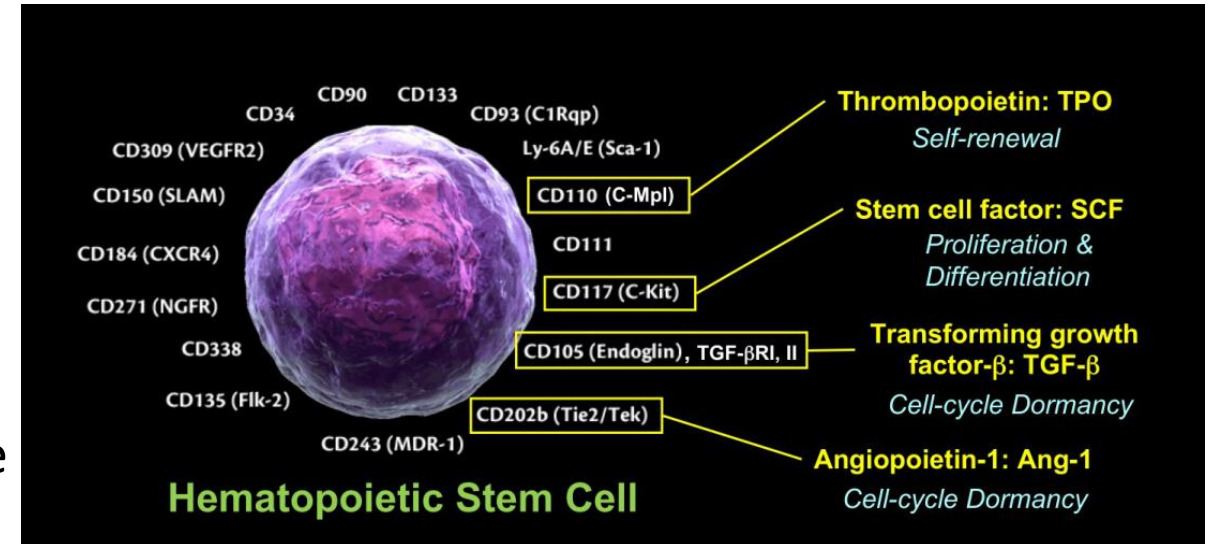
- Spleen – destruction of blood cells
- Liver – destruction of blood cells, proteins and amino acids collected
- Kidneys – proteins collected; amount of water regulated

Hematopoietic stem cells - HSC

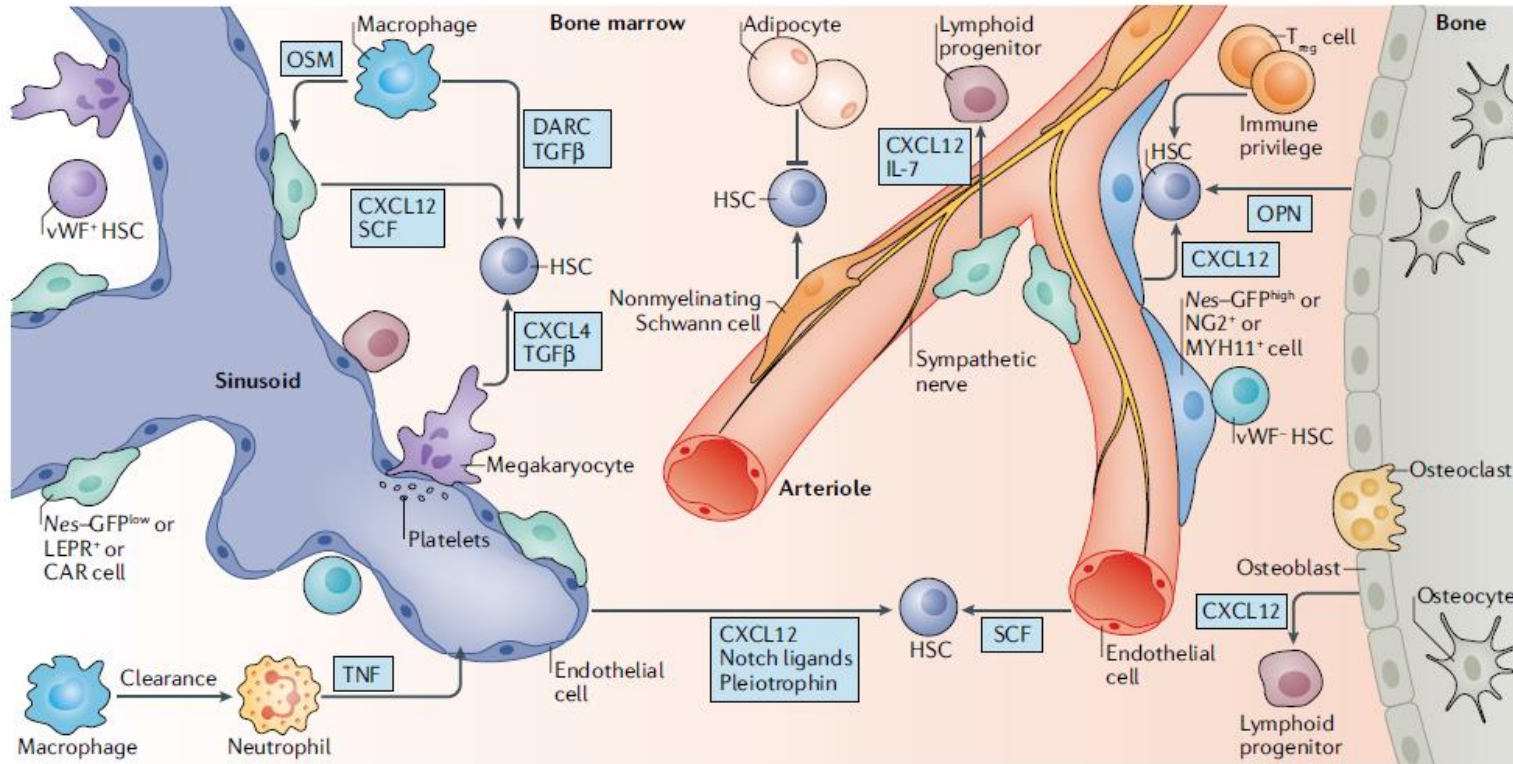
- Multipotent - capable of generating entire hematopoietic system
- Embryogenesis - aorto-gonado-mesonephros region, fetal liver
- Adults - bone marrow
- highly specialized rare cells
 - self renewal
 - differentiation into functional progenitors
- important for renewal after transplantation, infection, wound
- balance between differentiation and self renewal
- Intracellular factors
 - Regulators of transcription and epigenetics, metabolic pathways
- Extracellular factors
 - Humoral and neural signals, signals from the bone marrow niche

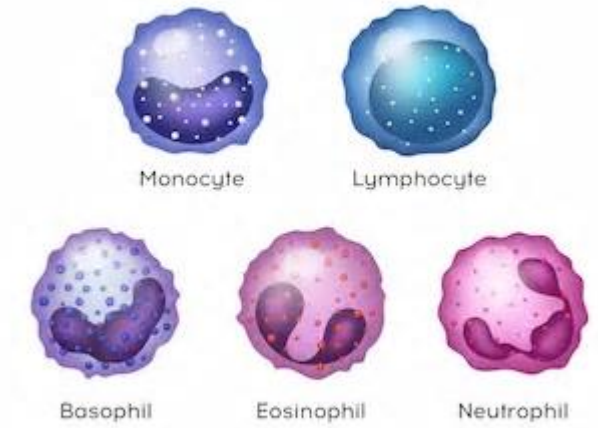
Hematopoietic stem cells - HSC

- 1:10 000 cells in the bone marrow
- Isolated based on Hoescht dye exclusion, resistance to 5-fluorouracil or γ irradiation
- Flow-cytometry – lack of CD markers of mature cells, expression of c-Kit (receptor for cytokine stem cell factor)
- Reside in specific niche in the bone marrow



Adult bone marrow in homeostasis

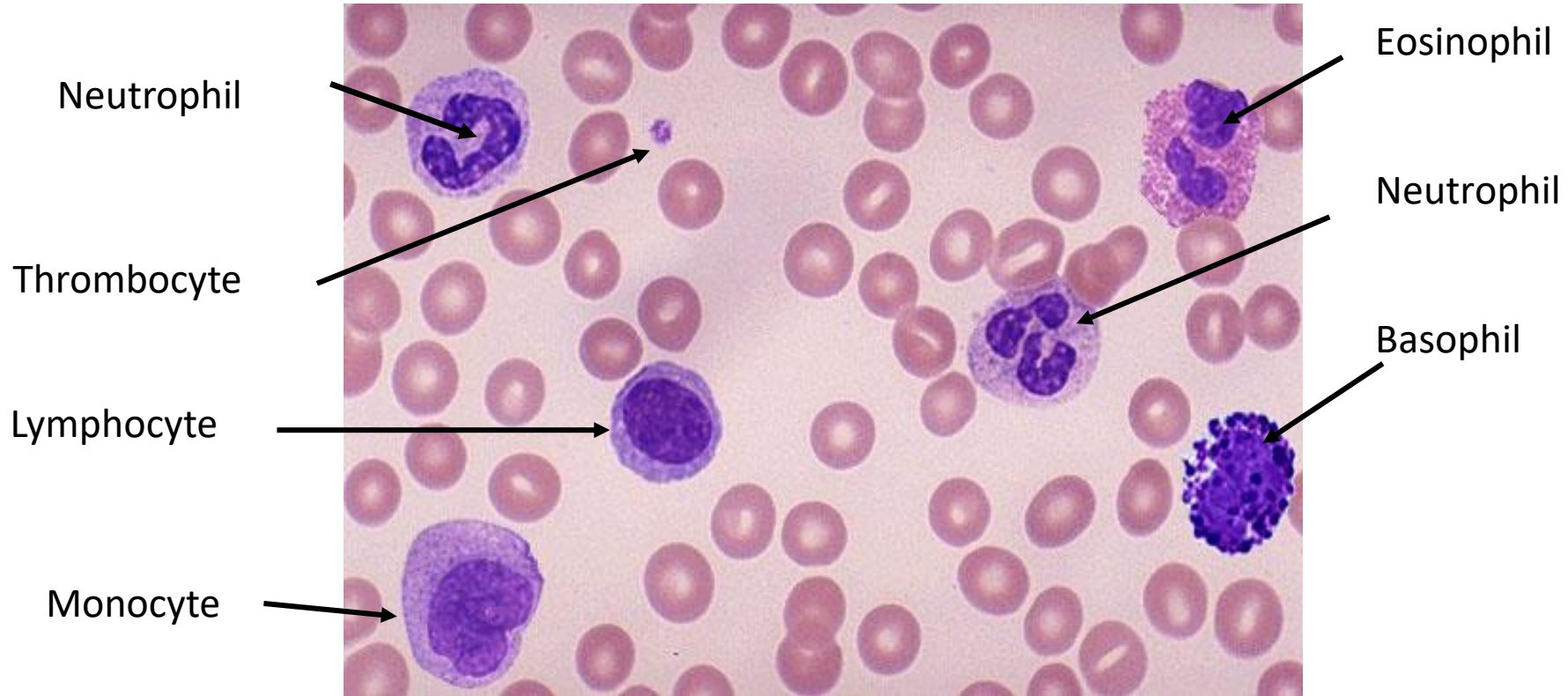




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II. Basic overview of blood cells

Blood smear

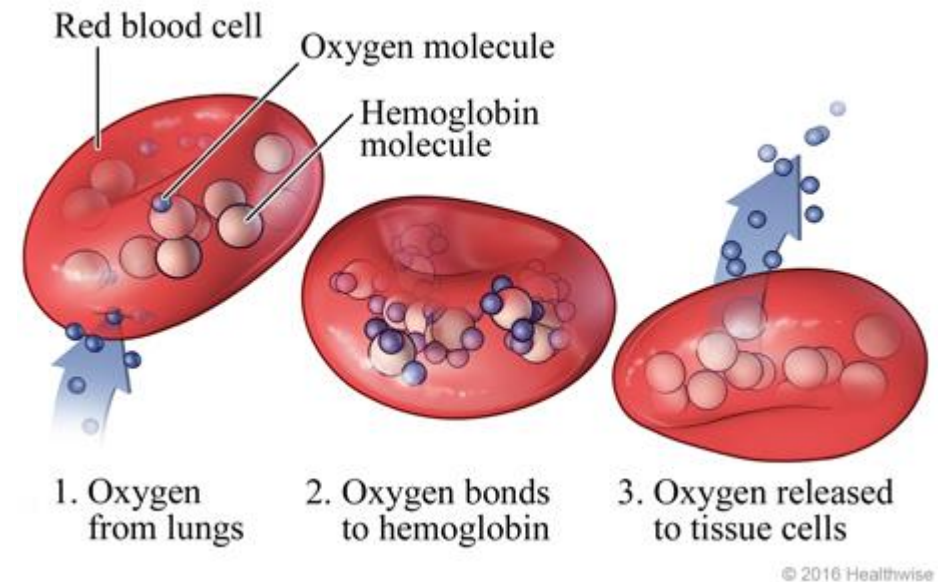


Erythrocytes

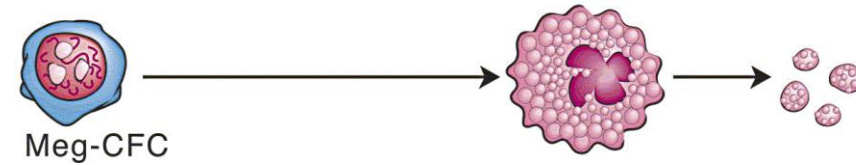
- Round, biconcave (larger area for gas exchange)
- no cell nucleus or organelles

Function

- transport of gases that are bound to hemoglobin inside erythrocytes
- transport of oxygen from lungs to the tissues, of CO₂ from tissues to lungs and out of the body



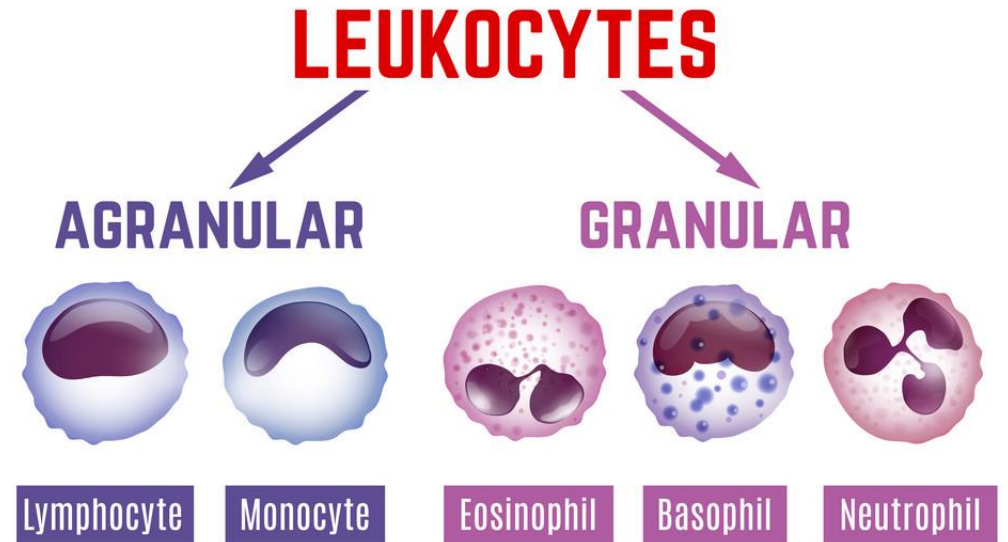
Thrombocytes



- small cells, oval shape, survive for four days, do not contain cell nucleus
- created by fragmentation of cytoplasm of large cells called megakaryocytes
- **Function**
 - ability to adhere and congregate
 - involved in coagulation, every time a blood vessel is injured
 - involved in the production of the thrombus that protects from large loss of blood

Leukocytes

- blood cells that are lighter in color and contain nucleus in comparison to erythrocytes
- divided based on size, shape of nucleus and function

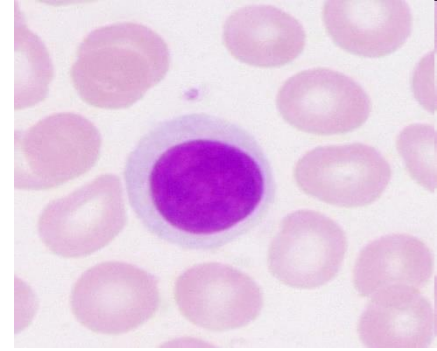


Leukocytes

- **Function**

- cells with ability to adhere, perform diapedesis and phagocytosis
- part of the immune system
- involved in a protective mechanism of the organism
- numbers increase in infections and inflammation

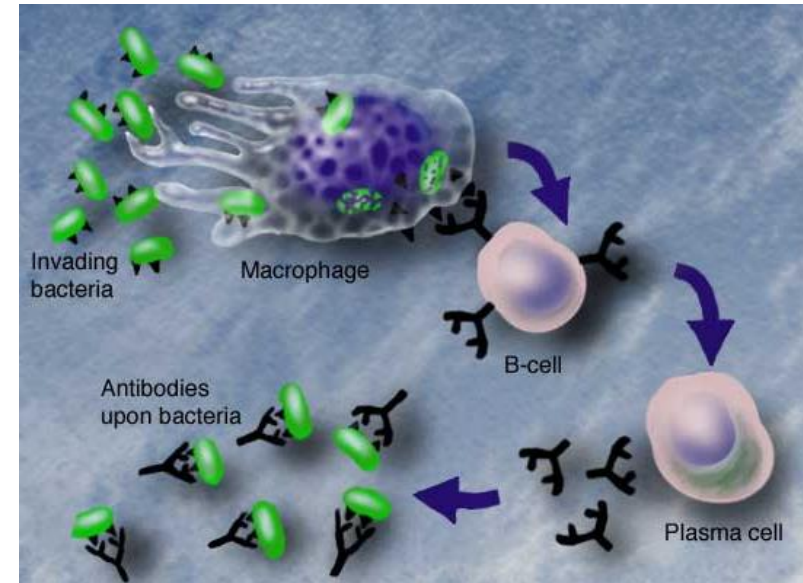
Lymphocytes



- round cells with a small amount of cytoplasm and one round nucleus
- two basic groups differing in function
 - T – lymphocytes (direct destruction)
 - B – lymphocytes (production of antibodies)
- **Function**
 - involved in specific immunity of the organism- antigen specific receptors
 - small fraction of lymphocytes - in peripheral blood, most are in the bone marrow, spleen, lymph nodes
 - after recognizing a foreigner particle, they start the protective reaction of the organism leading to destruction of the foreign particle

B-lymphocytes

- Originate and mature in the bone marrow, then migrate to lymph nodes, spleen and intestines
- after recognizing an antigen, they turn into plasma cells - production of antibodies (immunoglobulins - Ig)
- plasma cells migrate to peripheral blood, intestines, breast milk, tears etc



B-lymphocytes – production of antibodies

- to recognize and destroy foreign objects in the organism
- specific recognition of antigen based on a principle of a lock and key
- once an antibody reacts to specific antigen, a cascade is started leading to elimination of that pathogen
- Function of antibodies: opsonization, neutralization, complex formation
- 5 classes of antibodies:
 - IgG, IgA, IgM, IgE and IgD

Antibodies

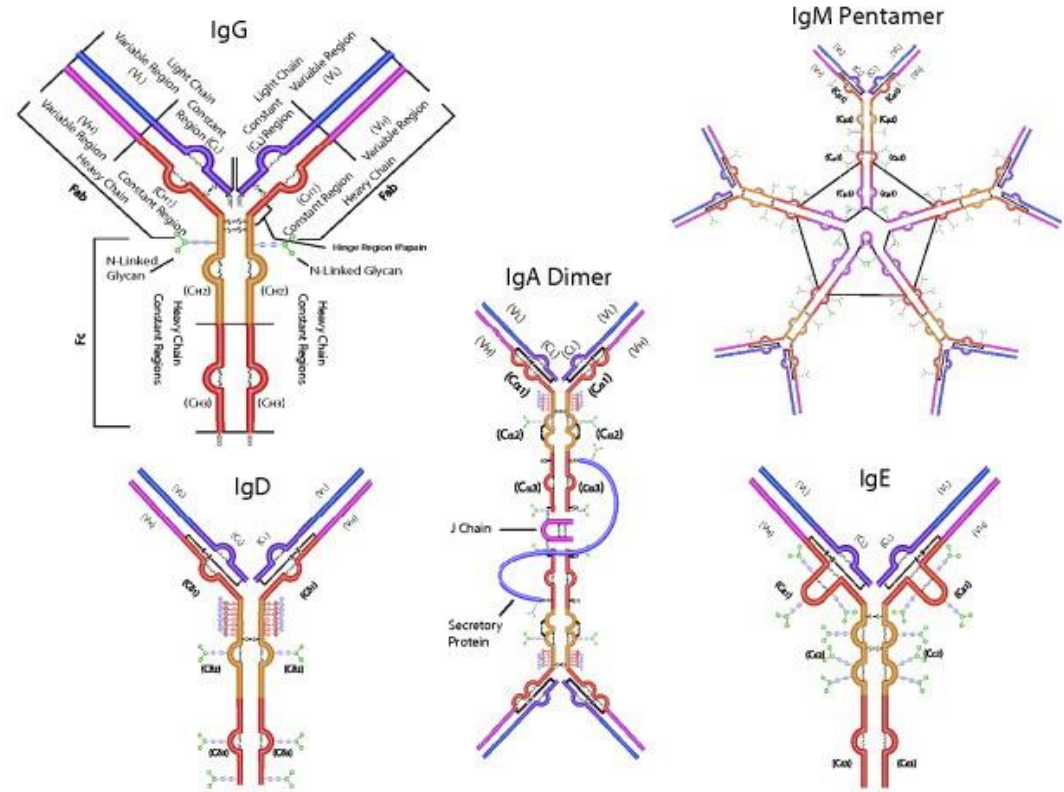
IgG antibodies are able to get into tissues and are the only ones that can enter the fetus through the placenta.

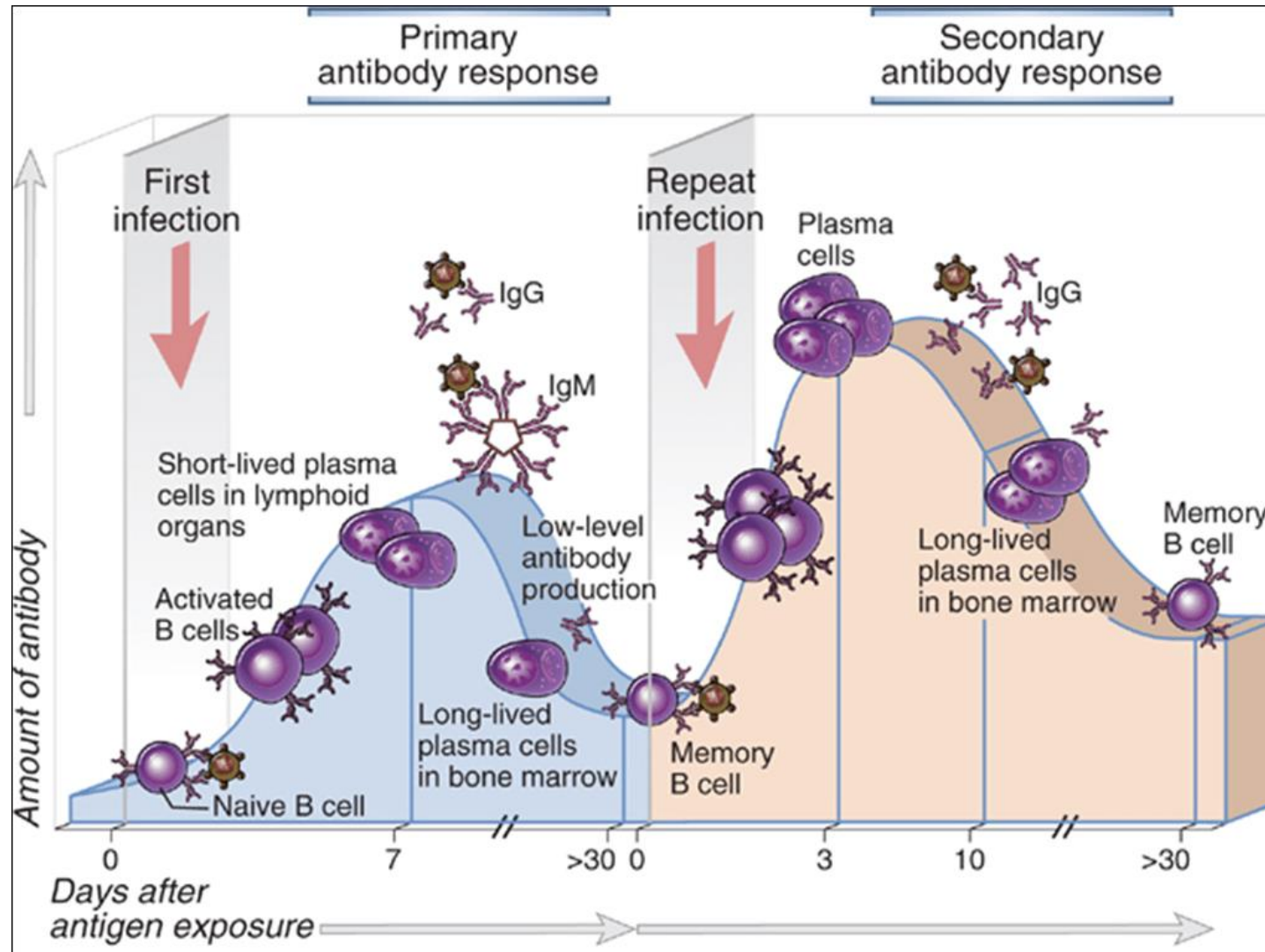
IgA antibodies are produced mainly in the mucous membranes of the intestine and breathing tube and protect the body from microorganisms entering the body

IgM antibodies are produced first during infection. They protect the organism within the first few days before other types of antibodies are produced

IgE antibodies are produced as a protection against parasites and are involved in allergic reactions

IgD antibodies are rare and are involved in histamine release





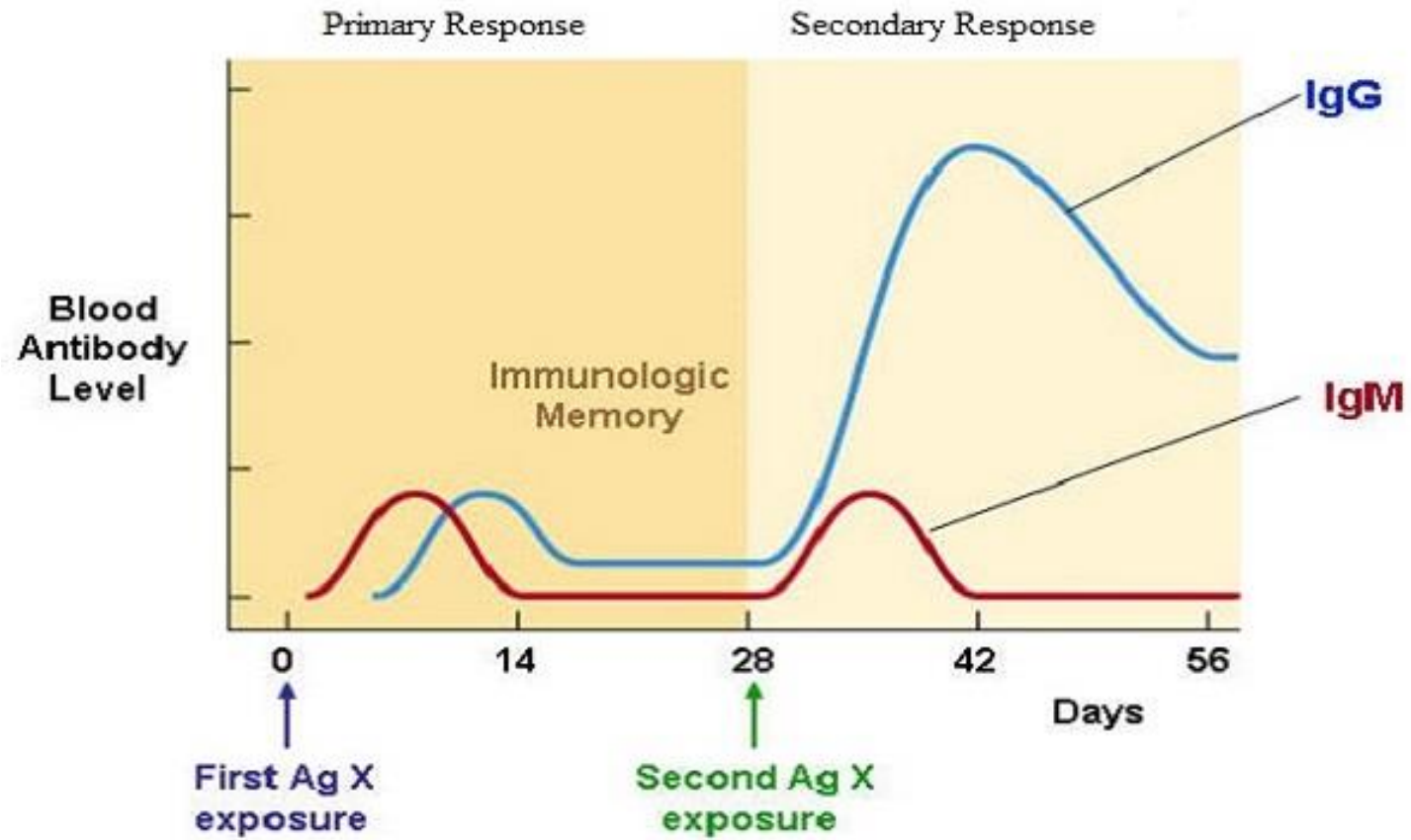
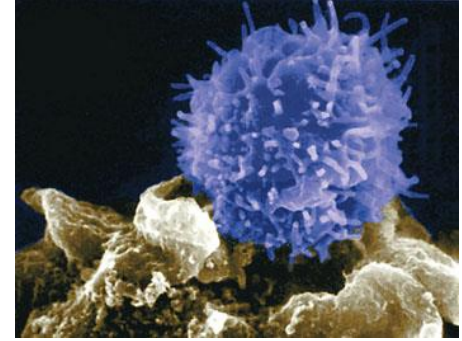


Fig. Immune Response and Secretion of antibodies

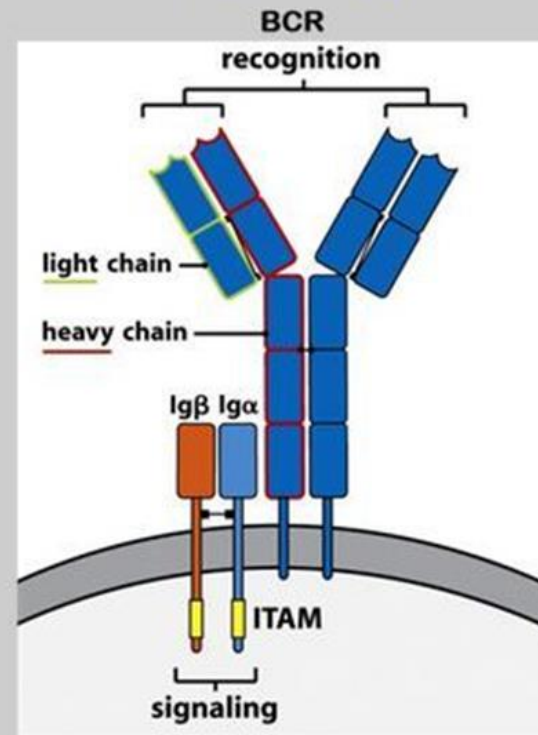
T lymphocytes



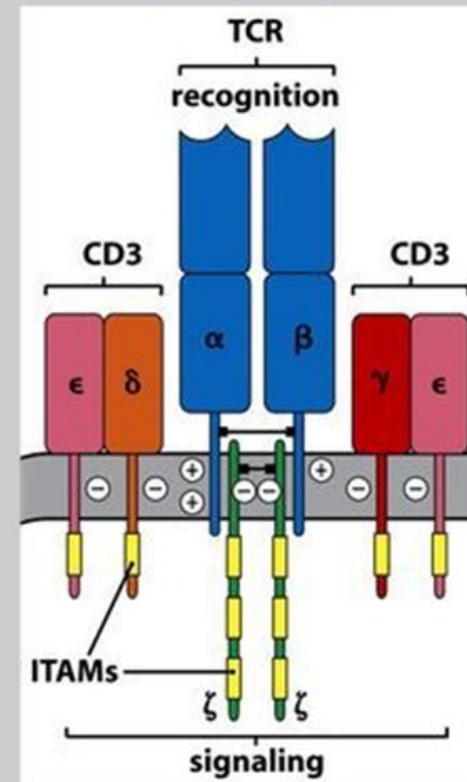
- Originate in bone marrow, thymus (if no thymus, no mature T cells)
- Mature T cells migrate to lymphoid organs, especially lymph nodes, spleen, bone marrow and peripheral blood
- Bind antigens using TCR receptors
- Unable to produce antibodies
- destroy cells that had been attacked by microorganisms
- regulate function of other immune cells

T Cell and B Cell Antigen Receptors (TCR and BCR)

B cell Receptor



T cell Receptor



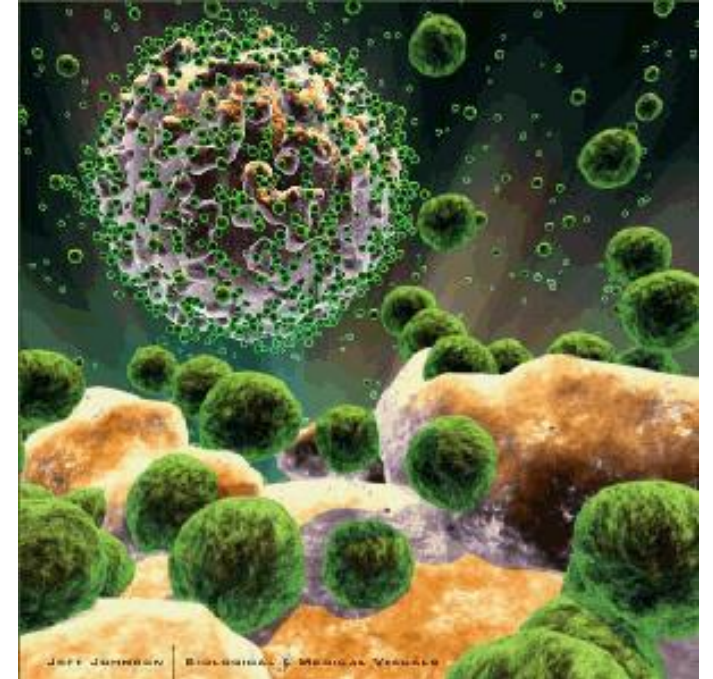
Classes of T cells

- **Cytotoxic** (Tc)
 - directly kill cells (some viruses are able to survive and duplicate inside cells. Infected cells need to be destroyed so that the infection does not spread)
- **Helper** (Th)
 - support the function of other cells of the immune system (Tc, B cells, macrophages)

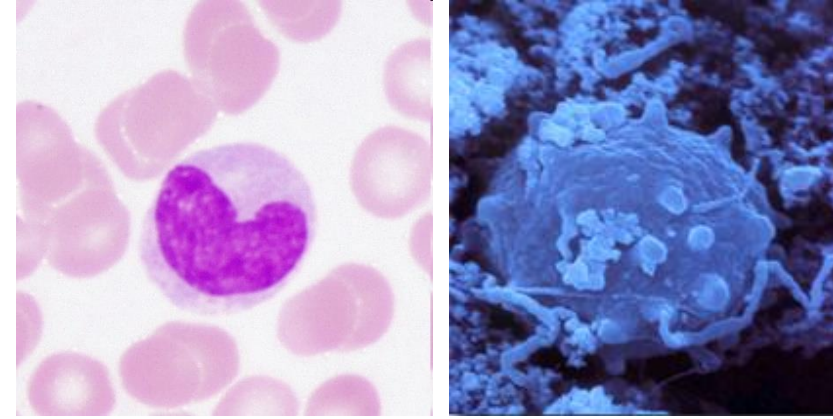
T – cells are target cells of HIV virus

HIV

- acquired immune deficiencies - immune system effected during the lifetime of an individual
- acquired immune deficiency syndrome (AIDS)
- HIV infects Th lymphocytes, macrophages and CNS cells
- after initial infection, virus survives in the body for several years without any symptoms
- then virus replicates - Th cells drastically decrease
- insufficient amount of Th cells leads to opportunistic infections (Kaposi sarcoma...)



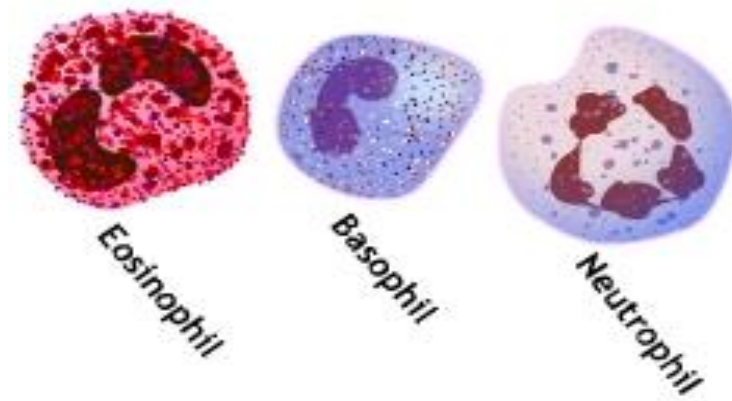
Monocytes



- large cells with a round or kidney shaped nucleus
- created in the bone marrow, migrate to peripheral blood where they circulate for about 8 hours
- then they enter tissues and change into macrophages

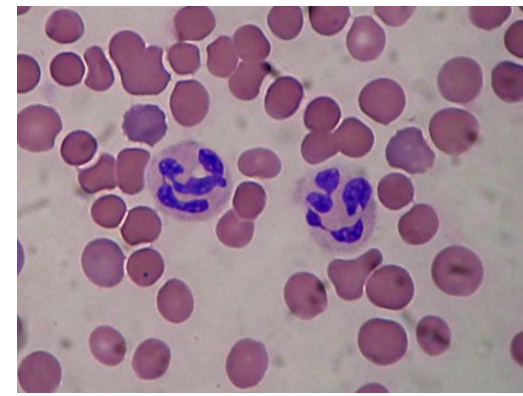
- **Function**
- monocytes and macrophages are part of the immune system
- the basic function of macrophages is the phagocytosis of bacteria, foreigner bodies or dead cells

Granulocytes



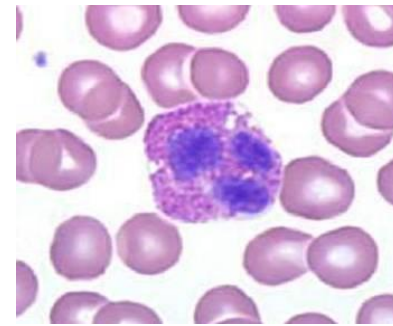
- Polymorphous nucleus - two to five segments
- cytotoxic granules in the cytoplasm
 - Neutrophil - pinkish purple granules
 - Eosinophil – orange-red granules
 - Basophils - dark blue granules
- **Function**
 - granulocytes are part of the non-specific immunity
 - involved in destruction of bacteria and parasites

Neutrophils



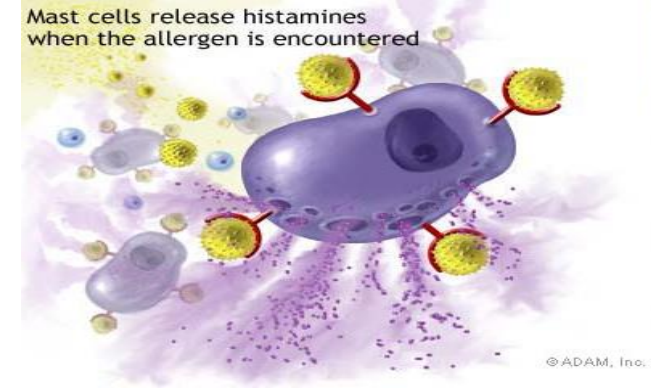
- Most common type of white blood cells with the shortest half life (12 hrs in blood, 1-2 days in tissues)
- Professional phagocytes - inflammation
- **Function:**
 - Phagocytosis (if opsonization, phagocytosis is easier)
 - Opsonization – process increasing effectivity of phagocytosis
 - Chemotaxis – ability to migrate to a place with highest concentration of bacteria
 - Diapedesis – ability to migrate from peripheral blood into the place of inflammation through the wall of the vein
- Perform phagocytosis only once, then they die

Eosinophils



- weak phagocytes
- main function is protection against parasites
 - Accumulate in places where parasites enter body (lungs, GIT)
 - Release granules that contain chemicals attacking the parasites
- involved in allergic reaction

Basophils



- Least common of all granulocytes and leukocytes
- Receptors for IgE on membrane
- Their granules contain heparin and histamine- inflammation and allergies
- Mast cells – in tissues and connecting tissues
- **Histamine**
 - Effects muscles, increases permeability of blood vessels
 - Massive release during allergic reaction