PSL301H:

Winter 2022

Human Physiology II

Week 1-2

Anlong Jiang

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Basics of Blood

FUNCTION OF BLOOD

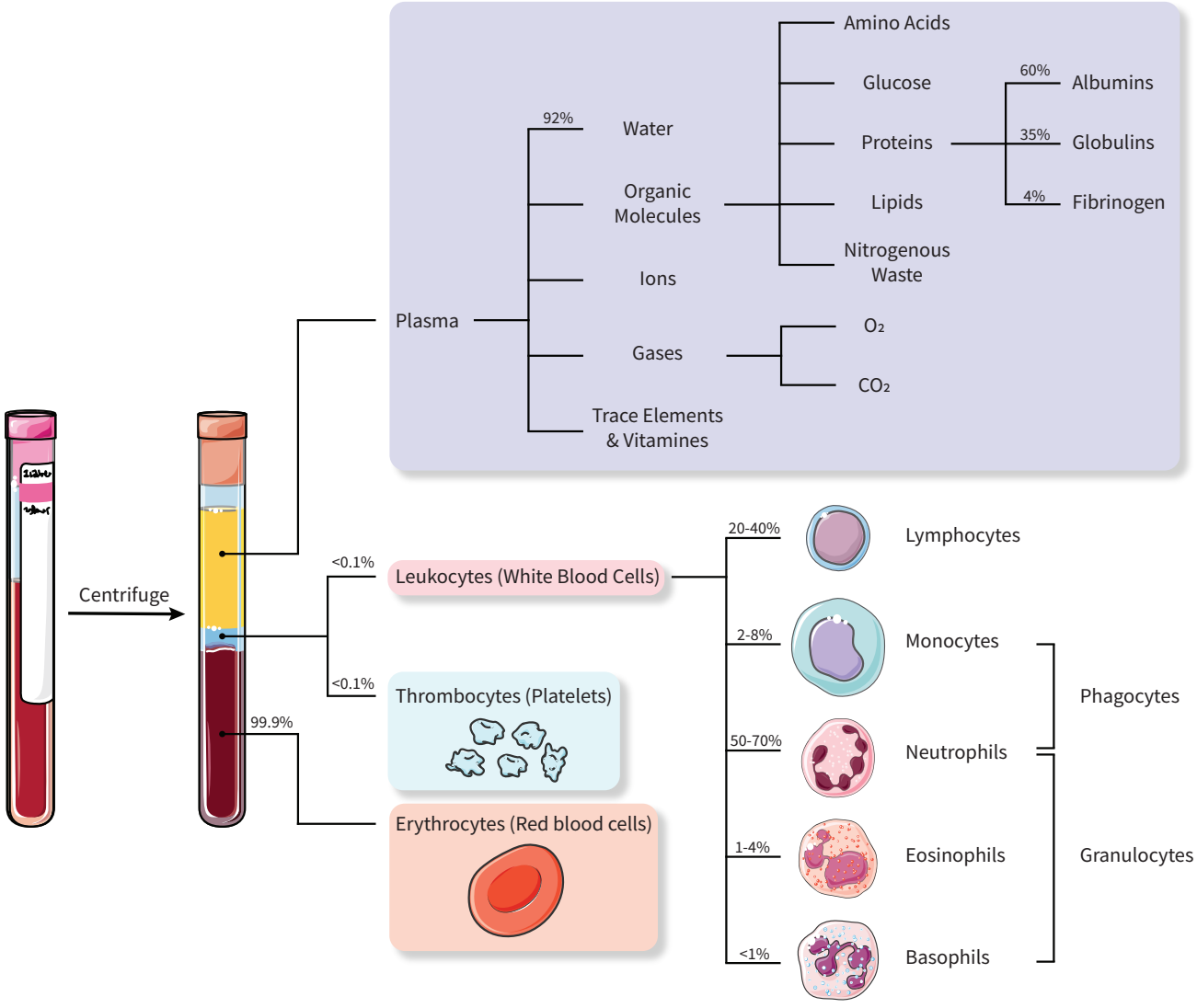
1. Transports gases, nutrients, hormones and metabolic wastes.
2. Regulates composition of interstitial fluid (e.g. pH, ions, water, etc).
3. Restricts fluid loss at injury sites via blood clotting.
4. Defends against toxins and pathogens.
5. Regulates body temperature by absorbing and redistributing heat.

COMPOSITION OF BLOOD

1. Cells
   a. Erythrocytes (Red blood cells)
   b. Leukocytes (White blood cells)
      i. Phagocytes: Can engulf small particles such as bacteria and dead cells.
      ii. Granulocytes: Contain granules (vesicles) in the cells.
   c. Thrombocytes (Platelets)

Hematocrit = % of total blood volume occupied by packed (centrifuged) red blood cells.

» Normal hematocrit = 37-54%.

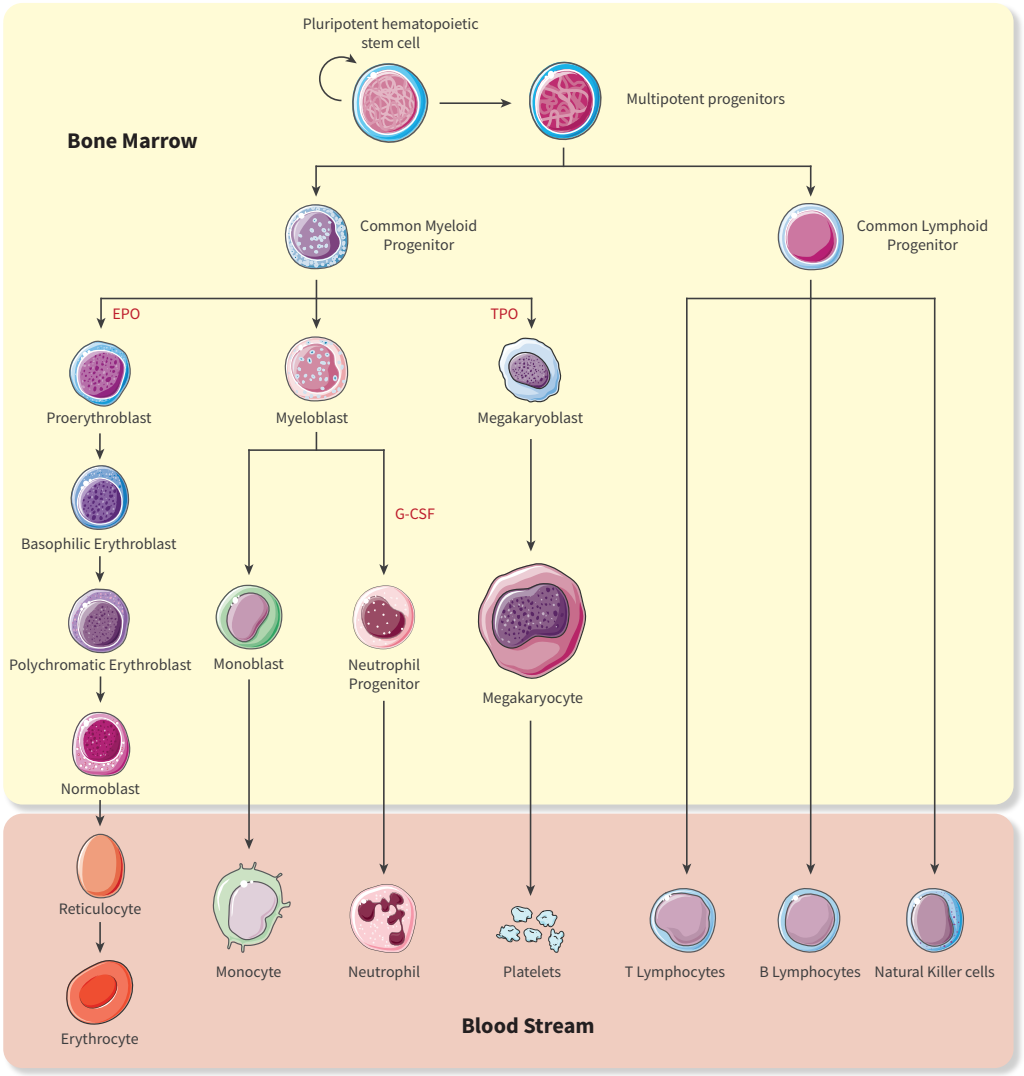


2. Plasma proteins
    a. General functions:
        i. Generate colloid osmotic pressure.
        ii. Buffer pH.
    b. Specific functions:

Proteins	Functions
Albumin	» Colloid osmotic pressure » Carrier proteins
Globulin α & β	» Cloting factors » Enzymes » Carrier proteins
Globulin γ	» Antibodies
Fibrinogen	» Forms fibrin for blood clotting

HEMATOPOIESIS

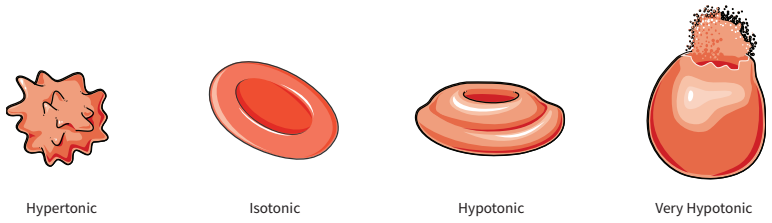
1. Definition: Hematopoiesis is the process of generating blood cells.



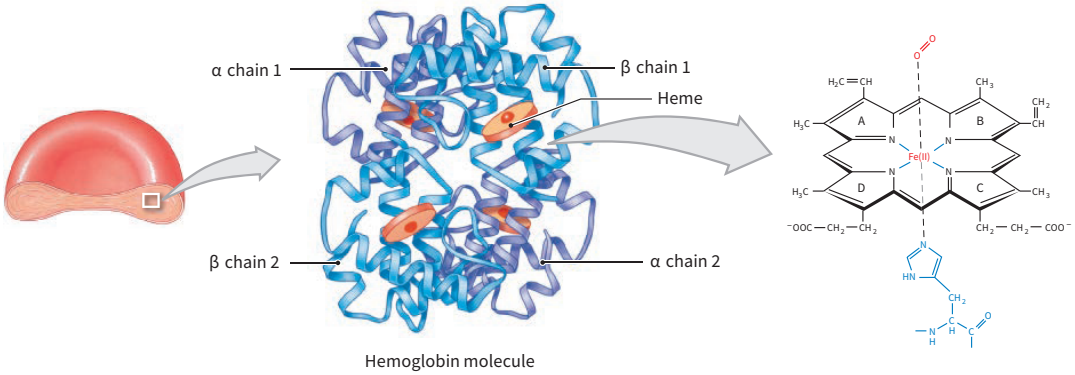
2. Location:
    a. Developing Embryo: Yolk sac, liver, spleen → bone marrow.
    b. After birth & Adult: Bone marrow: Pelvis, spine, ribs, cranium, proximal end long bones.
3. Regulation of hematopoiesis - Cytokines
    a. CSF (Colony Stimulating Factors): Stimulate the growth of leukocyte colonies.
    b. Interleukins (IL): Cytokines released by one white blood cell to act on another white blood cell.
    c. Erythropoietin (EPO): Produced by **kidney** and stimulate production of **erythocytes** in response to ↓[O_2].
        i. Low O_2 level stablize **hypoxia inducible factor (HIF1α)** wchich can activate transcription of EPO.
    d. Thrombopoietin (TPO): Produced by **liver** and stimulate production of **megakaryocytes**.

RED BLOOD CELLS

1. Basics of RBC
    a. Transport oxygen from lungs to tissues and carbon dioxide from tissues to lungs.
    b. Anaerobic metabolism:
        i. No nucleus in the cell (No new transcriptions), ejected when normoblast becomes reticulocyte.
        ii. No mitochondria and other organelles.
    c. Contains hemoglobins and enzymes.
2. Morphology



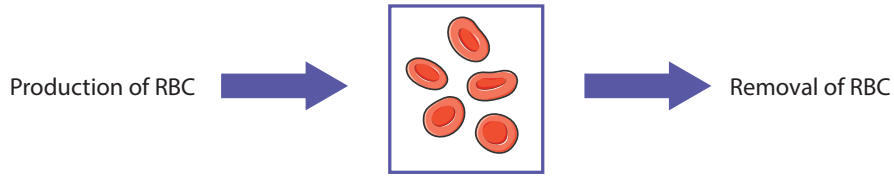
    a. Isotonic (Same osmotic pressure with plasma): Normal biconcave disk shape.
    b. Hypertonic (Higher osmotic pressure): Shink in size.
    c. Hypotonic (Less osmotic pressure): Swell in size and may burst in a very hypotonic solution leaving RBC ghosts.
3. Hemoglobin
    a. Hemoglobin consists of four globular protein (2α + 2β) subunits.
    b. Each subunit contains a single molecule of heme — a nonprotein ring surrounding a single ion of iron.
    c. Binding O_2 change its state from deoxy state to oxygenated state.
    d. Binding O_2 is a cooperative actiivty.



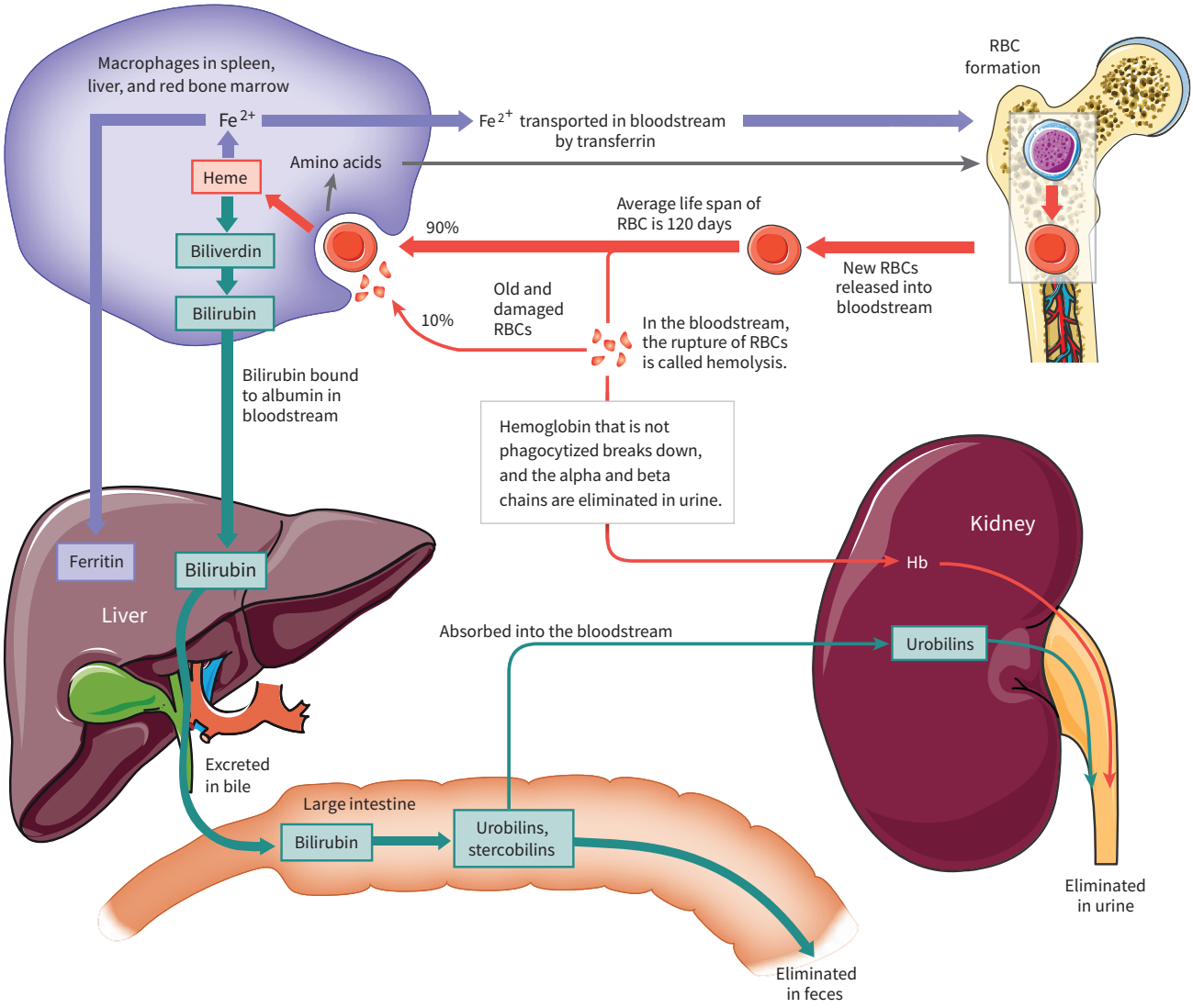
Hemoglobin molecule

TURNOVER OF RBC

RBCs are constantly produced and removed from human body under normal physiological conditions.



1. Production of RBCs is through hematopoiesis
2. Removal of RBCs:



ABNORMALITIES OF BLOOD

HYPERBILIRUBINEMIA (JAUNDICE)

Jaundice is a condition in which the skin and whites of the eyes become yellow and urine is dark yellow.

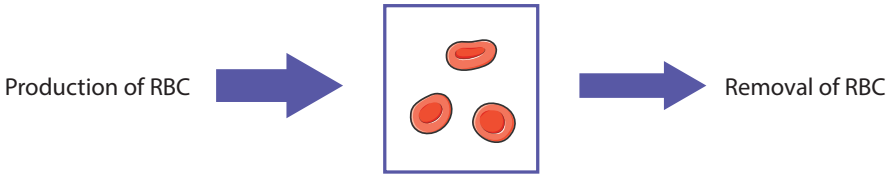
1. Symptoms:
    a. Yellowish discoloration of the **white area of the eye** and the skin.

2. Causes:
    a. High turnover of RBC
    b. Liver diseases
    c. Bile duct obstruction

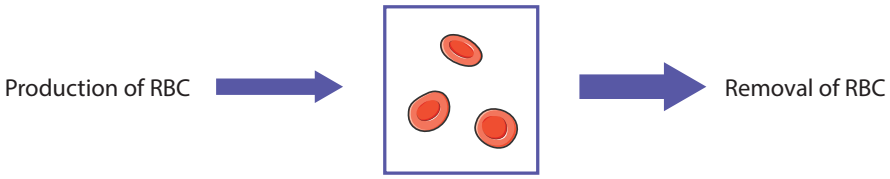
ANEMIA

A condition marked by a deficiency of red blood cells or of hemoglobin in the blood.

1. Symptoms:
    a. Irritability
    b. Fatigue
    c. Dizziness, lightheadedness, rapid heartbeat
2. Accelerated RBC loss



    a. Hemorrhage: Cells are normal in size and hemoglobin content but low in number.
    b. Hemolytic: Cells rupture at an abnormally high rate
        i. Genetic deficit: Membrane deficit, Enzyme deficit, and hemoglobin deficits (sickle cell anemia).
        ii. Aquired: Parasites infections (malaria), Drugs, and Autoimmune diseases.
3. Decreased RBC production

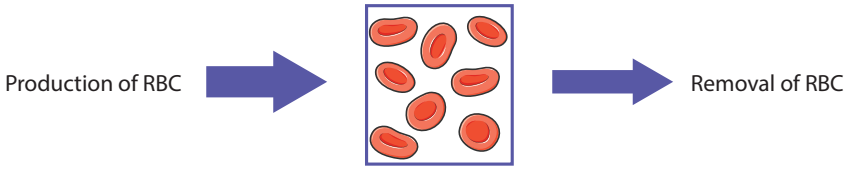


    a. Aplastic anemia:
        i. Drugs that affect the stem cells.
        ii. Radiation that destruct stem cells.
    b. Inadequate dietary intake of essential nutrients
        i. Iron deficiency → Low heme production.
        ii. Folic acid deficiency → Low DNA synthesis.
        iii. Vtamine B_{12} deficiency → Low DNA synthesis.
    c. Inadequate production of erythropoietin in kidney.

POLYCYTHEMIA

Polycythemia (polycythaemia or polyglobulia) is a disease state in which the hematocrit is elevated.

1. Symptoms:
    a. High blood viscocity.
2. Cause:



a. Primary polycythemia: Abnormal erythrocyte precursors.
b. Secondary polycythemia: Low oxygen delivery to tissues.

Pathogens & Overveiw of Immune System

PATHOGENS

A specific causative agent of disease.

Types of pathogens:

» Bacteria
» Viruses
» Fungi
» Parasites
» Protozoa

OVERVIEW OF IMMUNE SYSTEM

The system of the body that fights infection and disease and that includes especially the white blood cells and antibodies and the organs that produce them.

1. Lines of defense:
   a. Physical & chemical barriers.
   b. Innate immunity → **Rapid but non-specific**.
   c. Adaptive immunity → **Slower but specific**.
2. Tissues of immune system
   a. Tonsils
   b. Thymus
   c. Lymph nodes
   d. Spleen
   e. Bone marrow
   f. Gut-associated lymphoid tissue (GALT)
   g. Lymphatic vessels
3. Immune cells
   a. Lymphocytes
      i. B cells
      ii. T cells
      iii. Natural killer (NK) cells
   b. Monocytes & Macrophage

c. Neutrophils
d. Eosinophils
e. Basophils
f. Dendritic cells
g. Mast cells

LYMPHATIC SYSTEM

1. Functions of lymphatics
   a. Return excess tissue fluid to the blood.
   b. Transport pathogens/dendritic cells to lymph nodes.
   c. Transport fat from digestive system to the blood
2. Lymphoid organs
   a. Lymph nodes → Monitor lymphs.
   b. Spleen → Monitor blood.

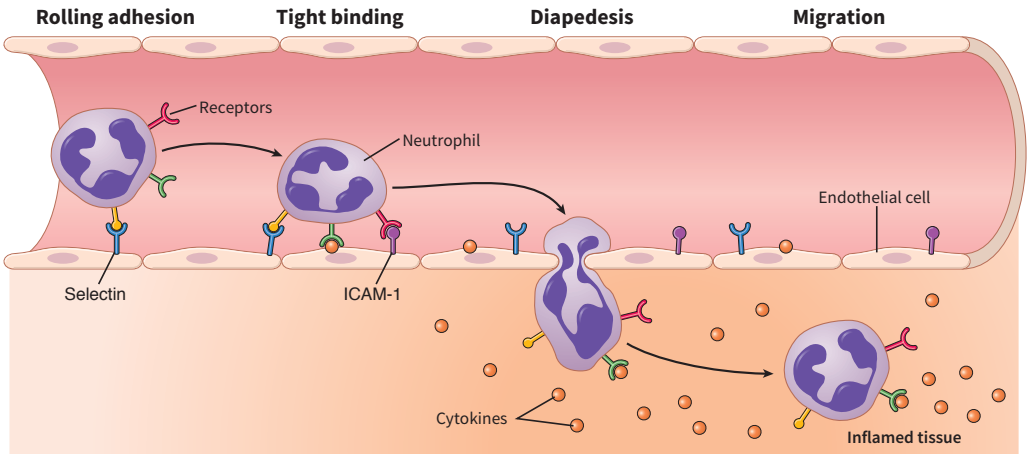
INNATE IMMUNITY

PHYSICAL BARRIERS

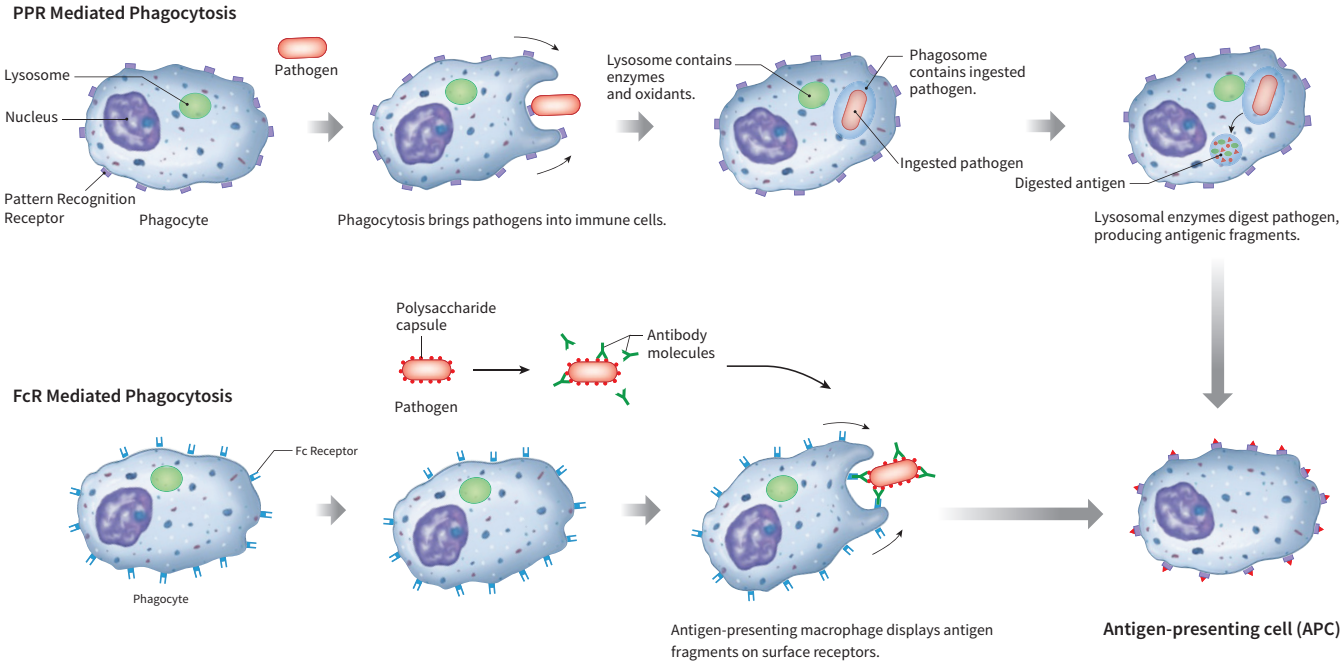
1. **Epithelium**: The protective barrier of skin and mucous membranes.
2. **Glandular secretions**: Salivary glands and the glands in airways secrete mucus and immunoglobulins to trap and disable inhaled or ingested pathogens.
3. **Stomach acidity**: The low pH of the stomach helps destroy swallowed pathogens.
4. **Mechanical removal**: Physical removal of pathogens
   a. Mucociliary escalator
   b. Tears
   c. Coughing, Sneezing
   d. GI mobility

PHAGOCYTES

1. Important classes of WBCs that act as professional phagocytes: macrophages and neutrophils.
2. Neutrophils are attracted to the site of inflammation by **chemotaxis**.

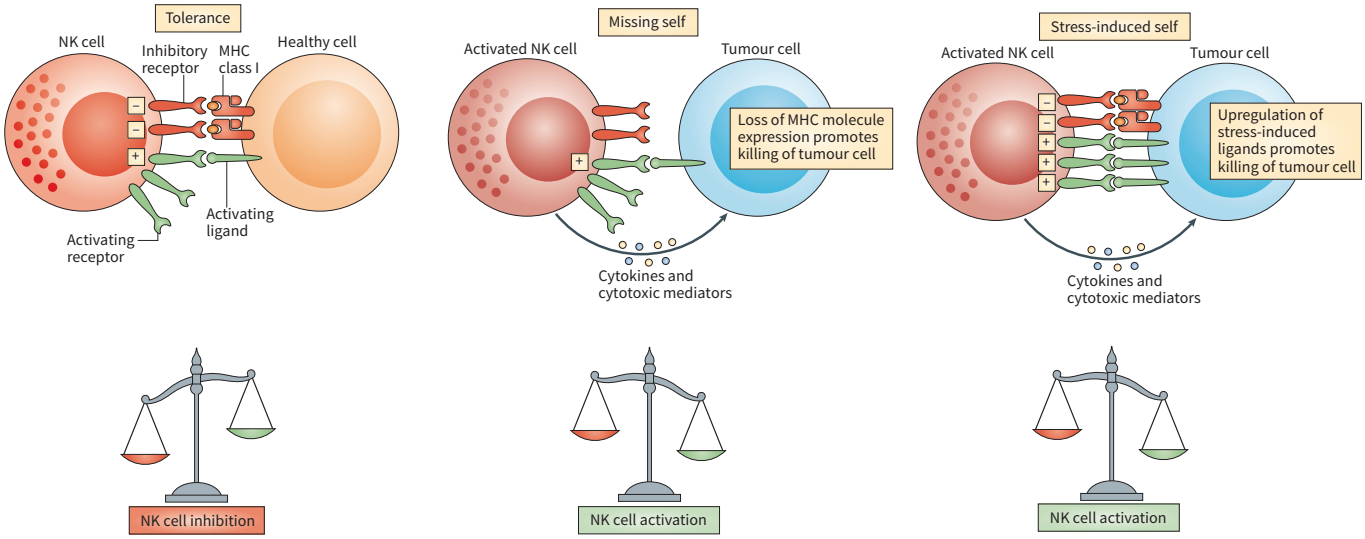


3. Phagocytosis of pathogens and antigen presentation
    a. Mediated by pattern recognition receptors (PRRs).
    b. Mediated by Fc receptors (antibody as **opsonin**).



NATURAL KILLER (NK) CELLS

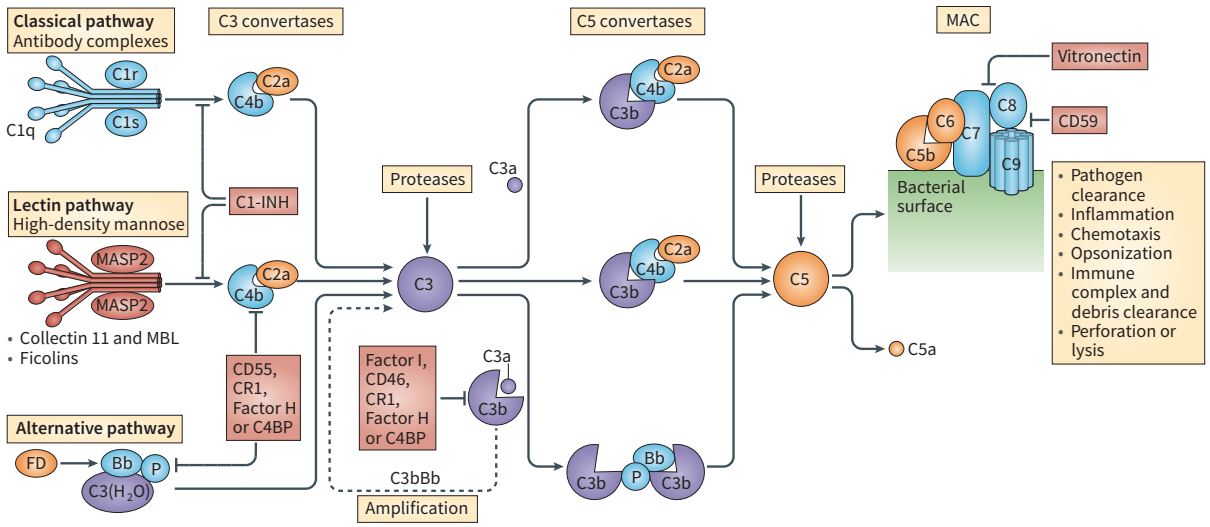
1. NK cells are used against virus infection or cancerous cells.
2. NK cells are regulated by many stimulatory and inhibitory receptor-ligand interactions at the same time.
    a. Activity determined by the **balance** between excitatioin and inhibition.



ANTIMICROBIAL PROTEINS

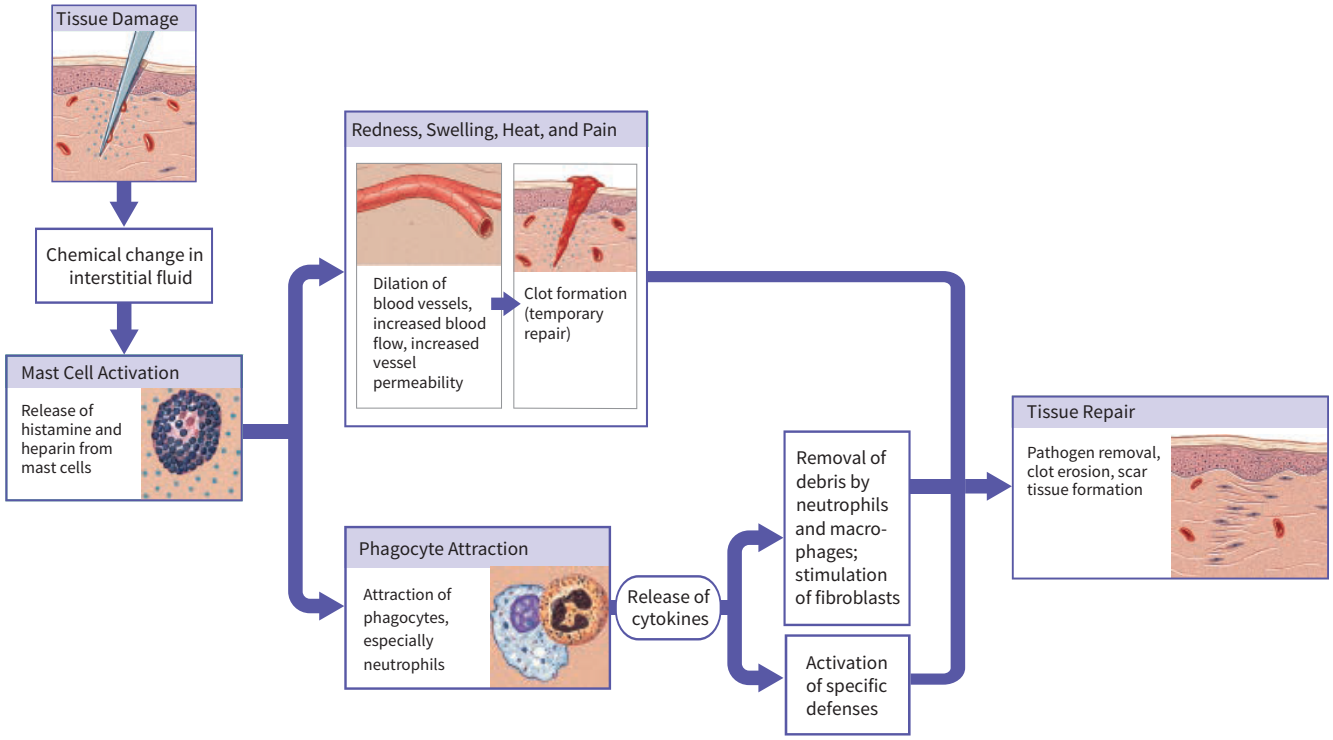
1. Interferon (IFN)
    a. Type I IFNs: IFN-α and β → Prevent viral replication in the cells.
    b. Type II IFNs: IFN-γ → Activate macrophages and other immune cells.

2. Complements
    a. Complements are soluble proteins in blood and other body fuild which are mainly produced by liver.
    b. Functions of complements:
        i. Destruct target cell membrane.
        ii. Stimulate inflammation.
        iii. Attract phagocytes.
        iv. Enhanve phagocytosis.
    c. Complements are initally inactive but can be activated via three pathways.



INFLAMMATION

1. Inflammation is a localized tissue response to injury.



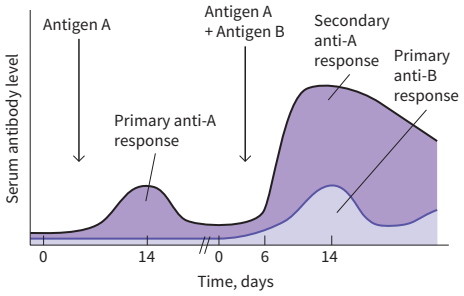
2. Symptoms:
    a. Swelling
    b. Redness
    c. Heat
    d. Pain
3. Functions of inflammatory response:
    a. Slowing the spread of pathogens.
    b. Mobilization of local, regional, and systemic defenses.
    c. Sets the stage for repair.

FEVER

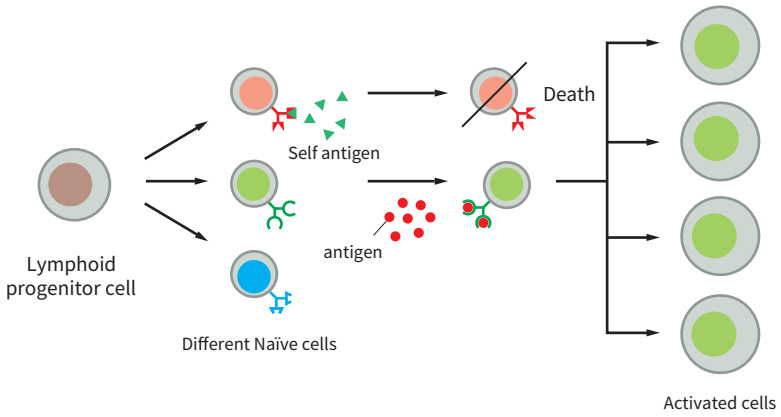
1. Fever is characterized by increased body temperature (> 37.2 °C).
2. Causes: Pyrogens change the thermoregulatory set point in the hypothalamus.
3. Functions of fever:
    a. Speeds up metabolic activity of host.
    b. Inhibits some pathogens.

Adaptive Immunity

1. Major players in adaptive immunity
    a. B cells → Originated in bone marrow and **matured in bone marrow** (Positive and negative selections).
        i. Produce antibody.
    b. T cells → Originated in bone marrow and **matured in thymus** (Positive and negative selections).
        i. Help and regulate other immune cells.
        ii. Kill infected cells.
2. Features of adaptive (aquired) immunity
    a. Specificity: Activated by and responds to a specific antigen.
    b. Versatility: Ready to confront any antigen at anytime.
        i. Huge repertoire of B cell receptors (BCRs), T cell receptors (TCRs) and antibody can be generated.
    c. Memory ability: “Remembers” any antigen it has encountered.
        i. The activated T and B cell can undergo clonal expansion.
        ii. Some cells are turned into memory cells which are long-lasting and continue to reproduce.
        iii. Secondary immune response is much quicker and more intense than primary immune response.



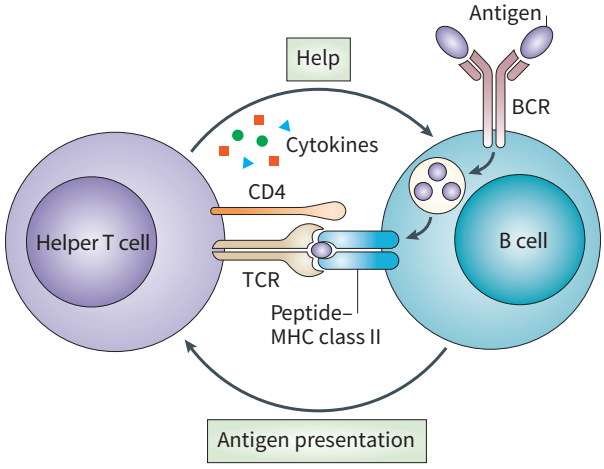
d. Tolerance: Responds to foreign substances but ignores normal tissues.



HUMORAL IMMUNITY

Humorla immunity is primary mediated by B cells.

1. B cell activation
   a. Thymus-independent (TI) antigen can directly activated B cell to effector B (plasma) cells.
   b. Thymus-dependeded activation requires help from Helper T cells (T_H).
      i. Antigen binds BCR and antigen presentation via MHC-II.
      ii. Interaction with T_H cells (MHC-II and TCR, CD40L and CD40).
      iii. Cytokines produced by T_H cells can enhance activation.



2. Antibody
   a. Functions of antibody
      i. Activate B cells.
      ii. Act as opsonins to tag antigens for phagocytosis.
      iii. Cause antigen clumping and neutralization of bacterial toxins.
      iv. Activate antibody-dependent cellular activity.
      v. Activate complement.
      vi. Trigger mast cell degranulation.

b. Classes of antibody

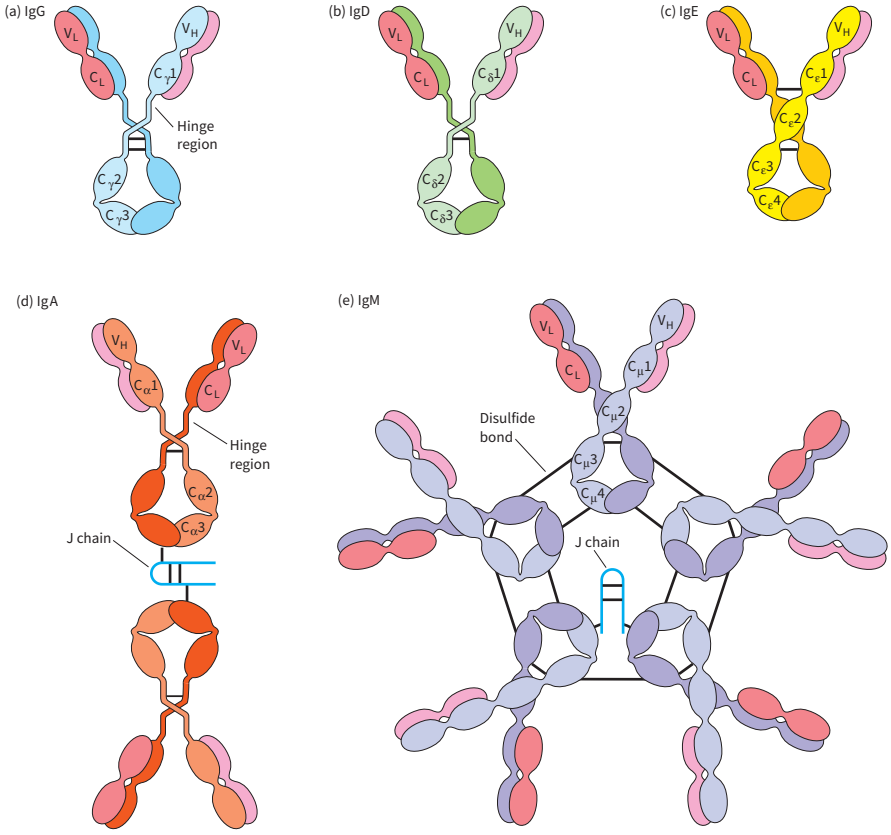
i. IgM → First antibody released in immune response with high avidity and is good at activating complement.

ii. IgA → Abundant in secretions and protect epithelial cells.

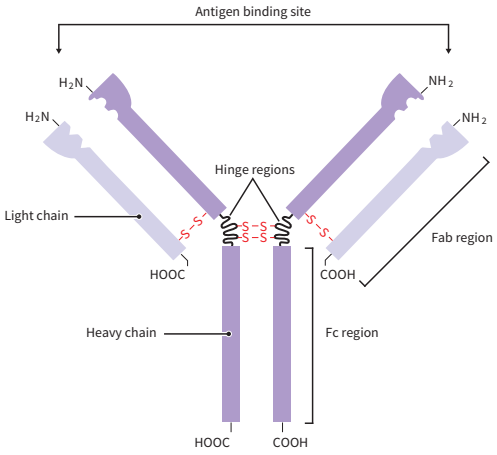
iii. IgG → Most common antibody and can be transfer across placenta.

iv. IgD → Major role as cell surface Ig.

v. IgE → Protect against parasite, can bind eosinophils and relate to allergic reactions.



3. Structure of IgG



1. IgG molecules have 2 heavy chains and 2 light chains.
2. 4 polypeptide chains are linked by disulfide bonds.
3. A single IgG molecule has two highly variable antigen binding sites.
4. 2 antigen binding arm is called Fab region and the bottom part is called Fc region.

4. Forms of immunity

a. Active immunity

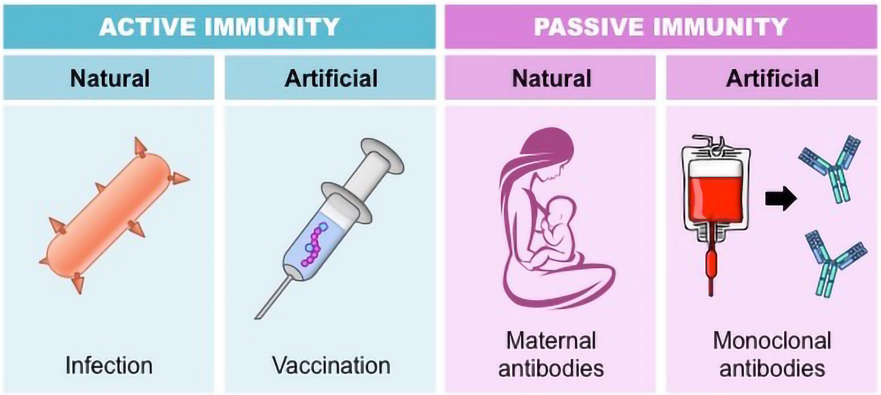
i. Naturally aquired:

ii. Artifically aquired

b. Passive immunity

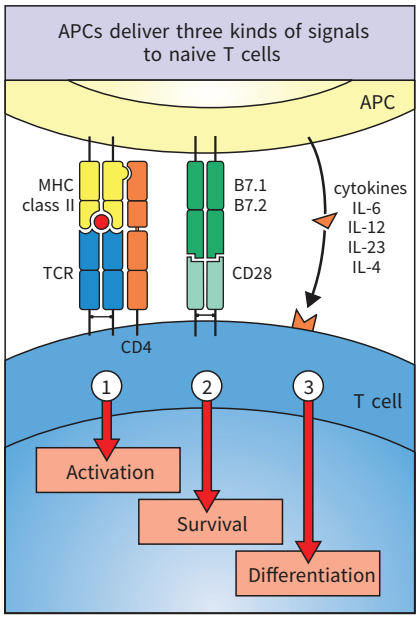
i. Naturally aquired

ii. Artifically aquired



CELL-MEDIATED IMMUNITY

1. Types of T cells:
   a. Helper T cells:
      i. Express CD4 on cell membrane ($CD4^+$).
      ii. Bind MHC Class II → Expressed on APC (Antigen presenting cells) → Present exogenous antigen.
      iii. Activate other T and B cells.
      iv. Release cytokines.
   b. Cytotoxic T cells
      i. Express CD8 on cell membrane ($CD8^+$).
      ii. Bind MHC Class I → Expressed on all nucleated cells → Present endogenous antigen.
      iii. Kill infected or cancerous cells.
2. Activation of T cells

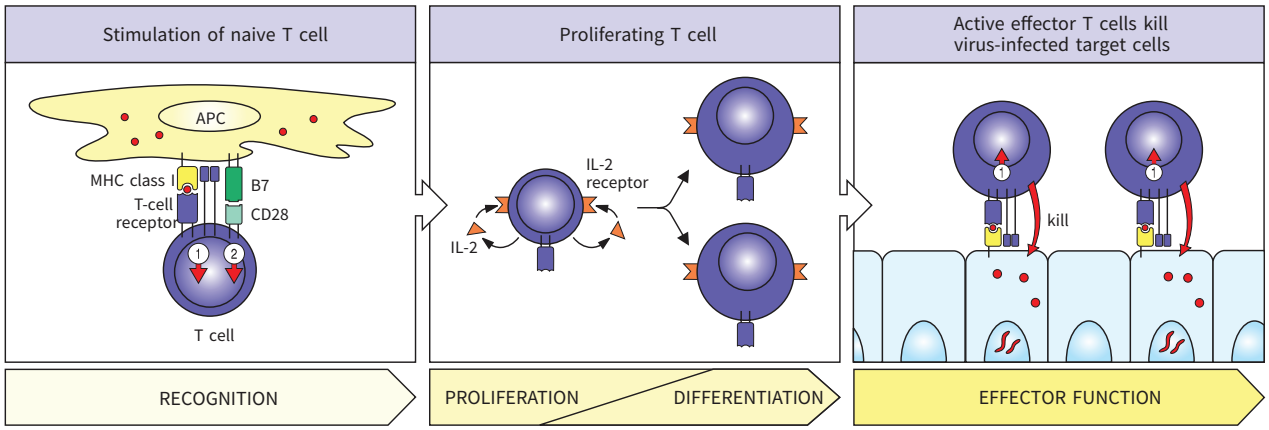


Three signals are required to activate T cells by antigen presenting cells:

1. Interaction between TCR and MHC class II.
2. Interaction between CD28 and B7.1 + B7.2.
3. Cytokine released by APC.

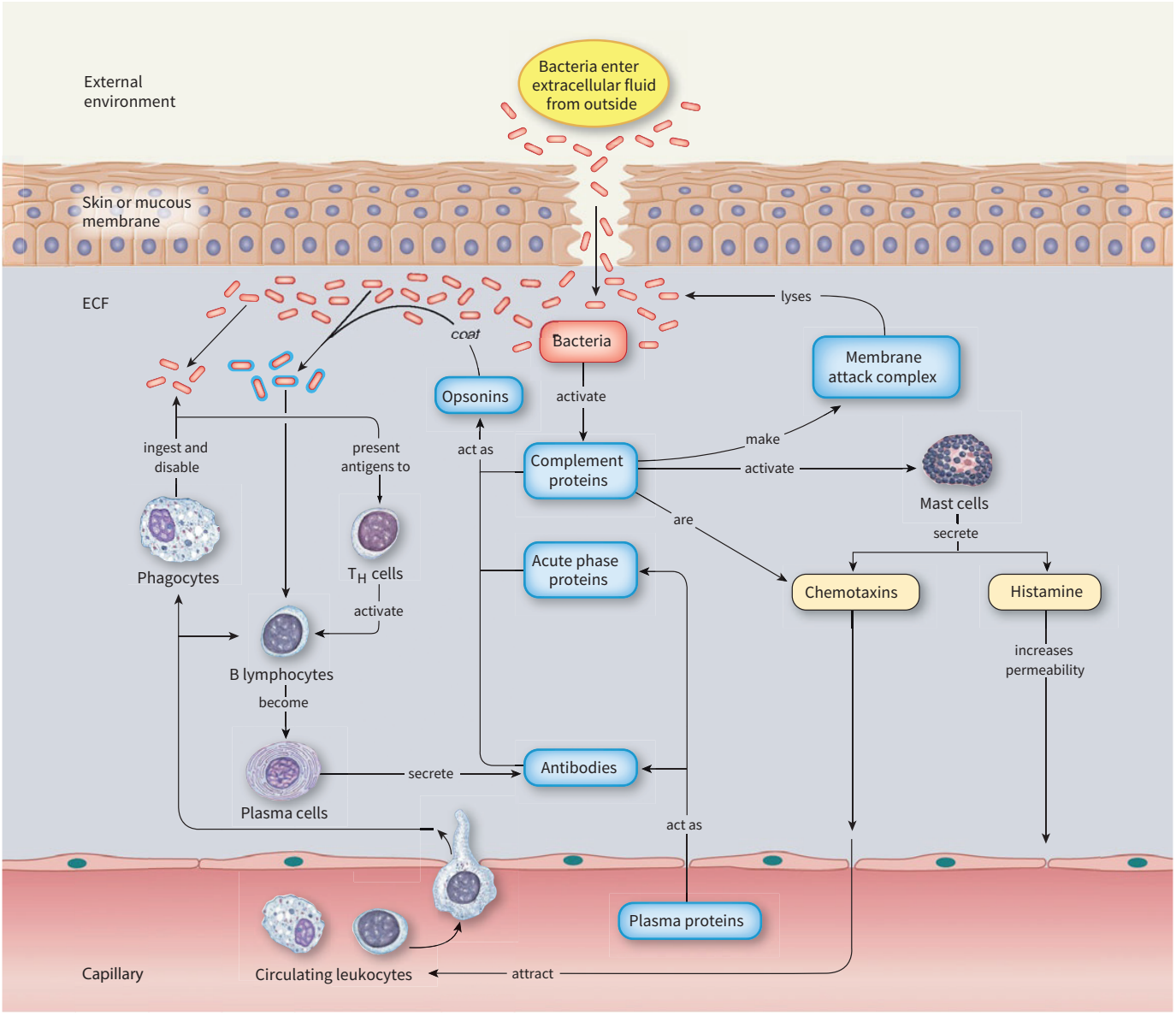
Note: Lack of Singal 2 will lead to T cell anergy.

3. Effects of cytotoxic T cells.



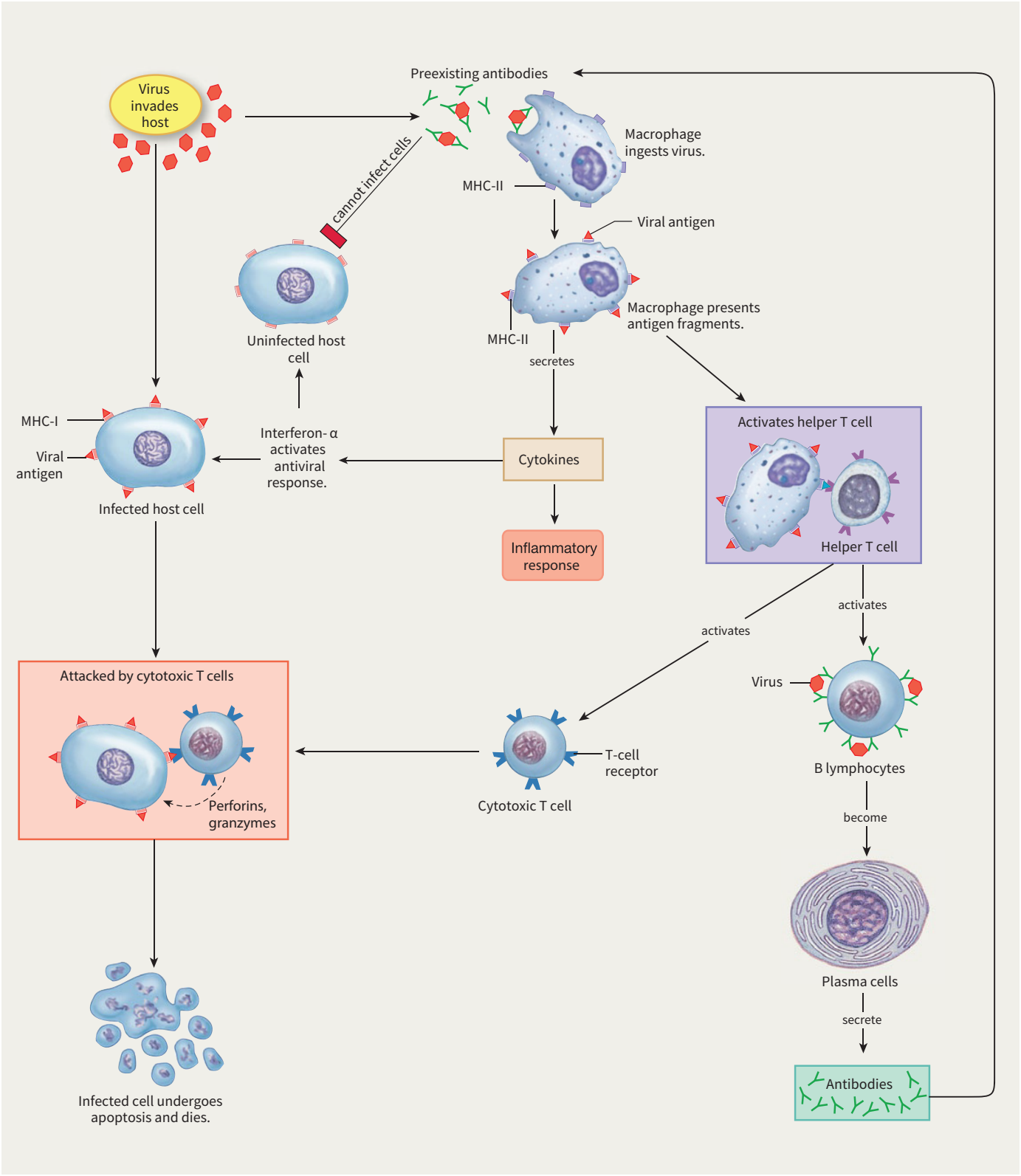
BACTERIA INFECTION SUMMARY

1. Bacteria infection is usually in the extracellular region.
2. Primary immune response is mediated by humoral immunity.



VIRUS INFECTION SUMMARY

1. Virus can distribute in extracellular region and infect living cells.
2. Trigger both humoral and cell-mediated immune response.

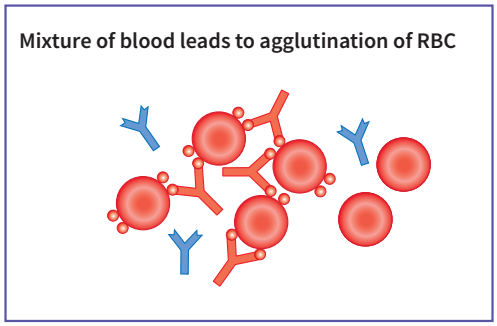


BLOOD TYPE & DONATION

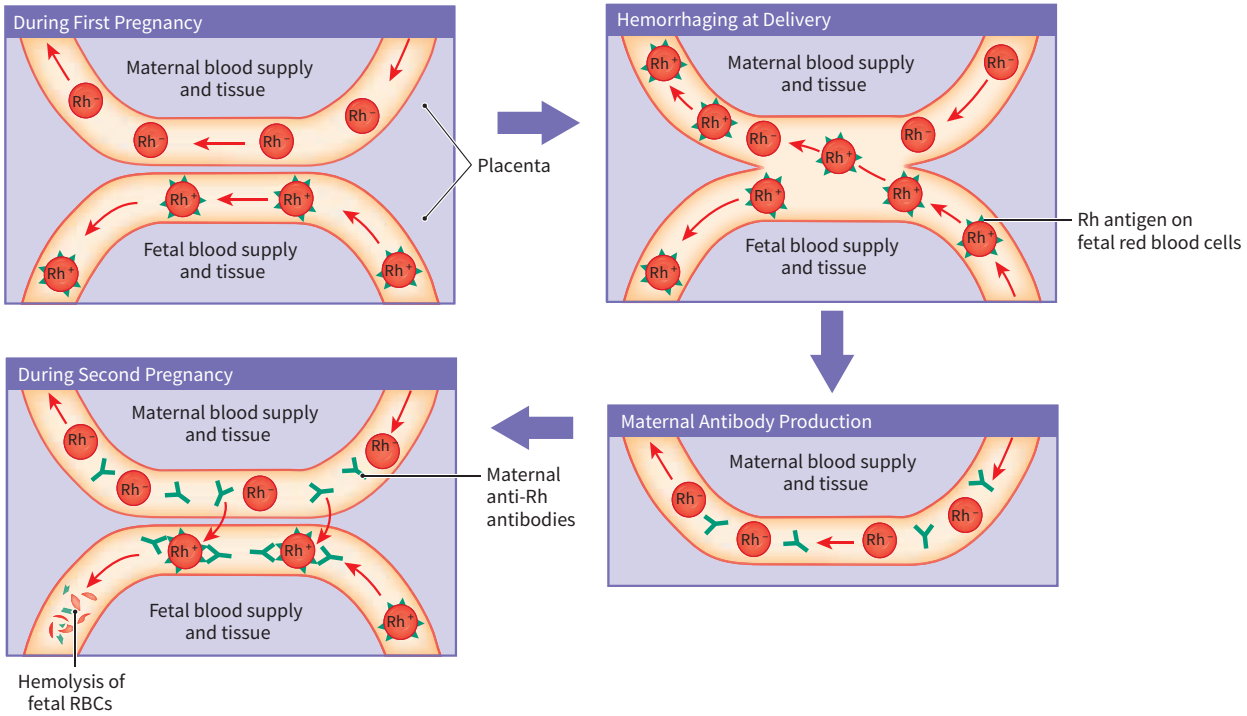
There are two major systems of blood types:

1. ABO blood group

Blood Type	Antigen on RBC	Antibodies in Plasma
O	No A or B antigens	"Anti-A" and "anti-B"
A	A antigens	"Anti-B"
B	B antigens	"Anti-A"
AB	A and B antigens	None to A or B



2. Rh (Rhesus) blood group
   a. Rh^+: Rh positive → Rh antigen on RBCs.
   b. Rh^-: Rh negative → No Rh antigen on RBCs (Usually not have anti-Rh antibody).
3. Hemolytic disease in newborn (HDN)
   a. Hemolytic disease in newborn is due to the incompatibility between mother and baby.
   b. Hemolytic disease will cause anemia, jaundice, enlarged spleen and liver, and severe edema.

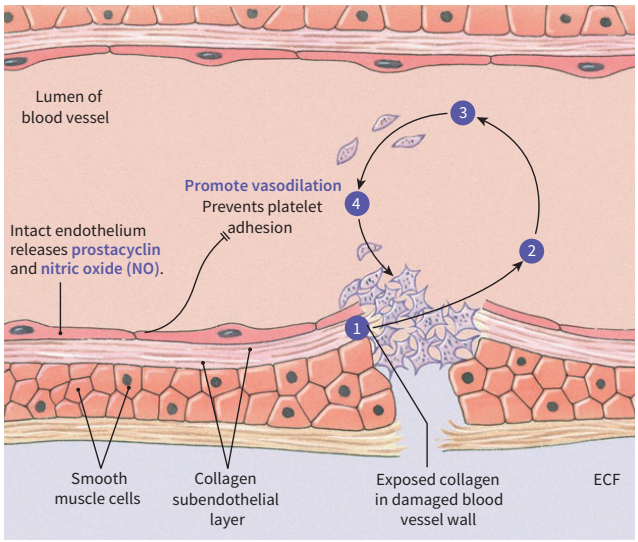


c. Prevention → **Inject anti-RhD antigen antibodies into Rh⁻ mother during and following her pregnancy**.
   i. The antibody will bind and remove fetus RBCs before they can trigger mother's immune response.
   ii. Mother will not produce any anti-RhD antibody.

Blood Hemostasis

BLOOD CLOTTING

1. **Vascular phase → Vasoconstriction**
   a. Neurogenic and myogenic control
   b. Vasoconstrictive paracrines prolong this action:
      i. Serotonin (platelets)
      ii. Thromboxane A_2 (platelets)
      iii. Endothelin-1 (endothelial cells)
2. Platelets phase → Platelets adhesion to the damaged site



Steps in the platelet phase

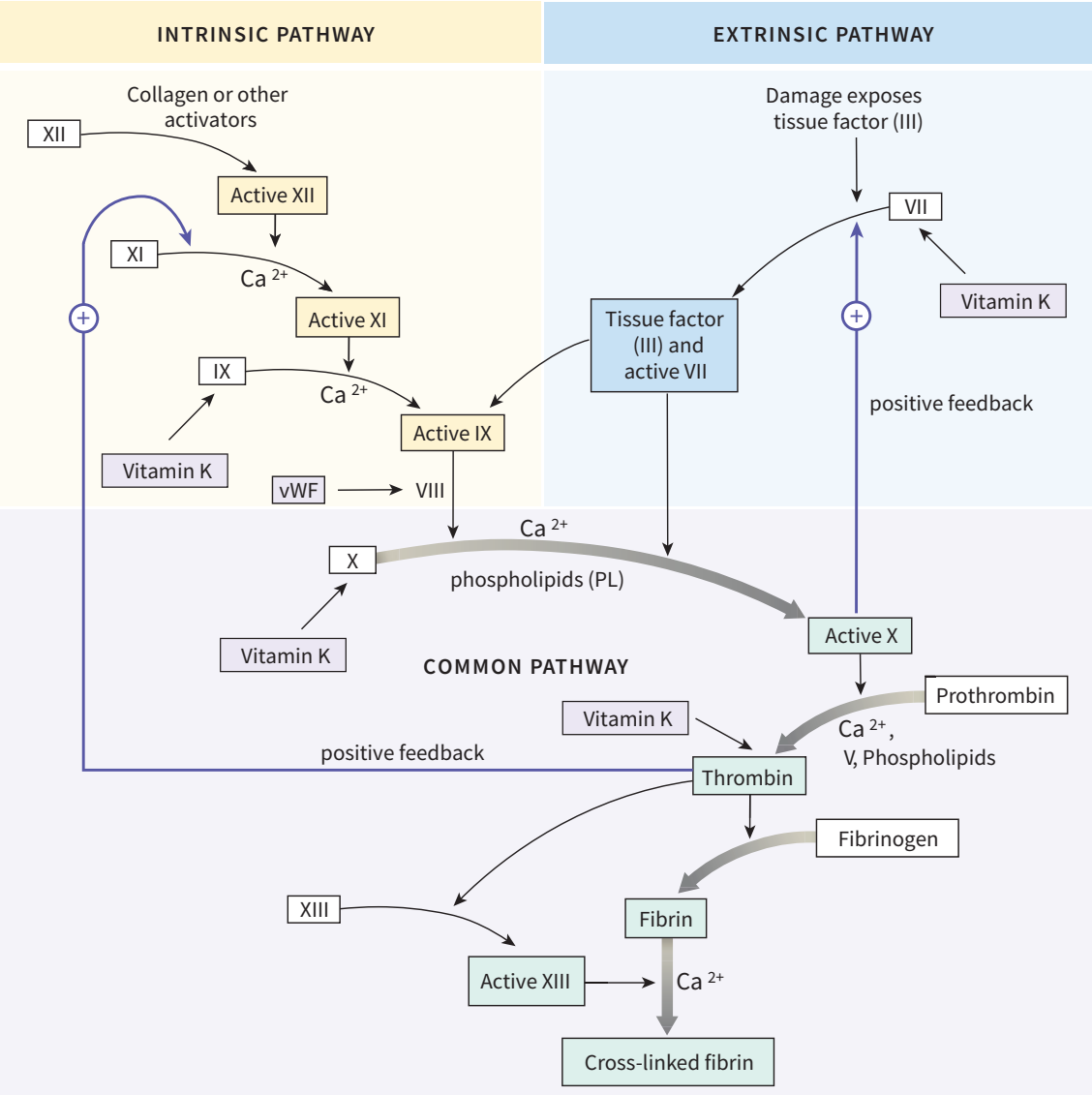
1. Exposed collagen on blood vessel binds and activates platelets via von Willebrand factor (vWF).
2. Platelets get activated and release platelet factors:
   a. ADP
   b. Platelet-activating factor (PAF)
   c. thromboxane A_2
   d. Serotonin
3. More platelets will be attracted to the damaged site.
4. Aggregation of platelets to form plug.

3. Coagulation cascade
   a. Extrinsic pathway
      i. The extrinsic pathway is initiated by factors external to the blood.
      ii. Initiated by thromboplastin (tissue factor III).
   b. Intrinsic pathway
      i. The intrinsic pathway requires only clotting factors found within the blood itself.
      ii. Intrinsic pathway needs more steps and usually slower than extrinsic pathway
   c. Common pathay
      i. Extrinsic pathway and intrinsic pathway will converge to common pathway.
      ii. Central factor is the Factor X.
      iii. Activation of pro-enzyme to active enzyme.
      iv. Activation of fibrinogen will cause crosslink of fibrin.

d. Anti-coagulant

i. Coumadin (Warfarin): Block Vitamin K and hence interrupt the synethsis of VII, IX, X and thrombin.

ii. EDTA: Chelator of divalent ion Ca^{2+}.



CELL-BASED THEORY OF COAGULATION

1. Initiation phase
   a. Cell with tissue factor on the cell surface is the primary physiologic initiator of coagulation.
   b. Factor VII in plasma binds tightly to cellular TF and is rapidly activated by coagulation.
   c. The factor VIIa/TF complex activates both factor X and factor IX.
   d. Small amounts of thrombin is produced.
2. Amplification phase
   a. Platelets adhere to extravascular matrix components at the site of injury.
   b. Small amounts of thrombin generated on TF-bearing cells amplify the initial procoagulant signal by enhancing platelet adhesion.
   c. Thrombin activates factors V, XI, and VIII on surface of platelets.

3. Propagation phase
    a. Active factors on the surface of platelets form tenase and then prothrombinase results in large amounts of thrombin.
    b. Thrombin cleaves fibrinogen and factor XIII to result in fibrin formation and cross-linking.

CLOT REMOVAL

1. Clot disintegrates when fibrin is broken into fragments by the enzyme plasmin
2. Thrombin, a factor in the coagulation cascade, works with a second factor called tissue plasminogen activator (tPA) to convert inactive plasminogen into plasmin.
3. Plasmin then breaks down fibrin, a process known as fibrinolysis.