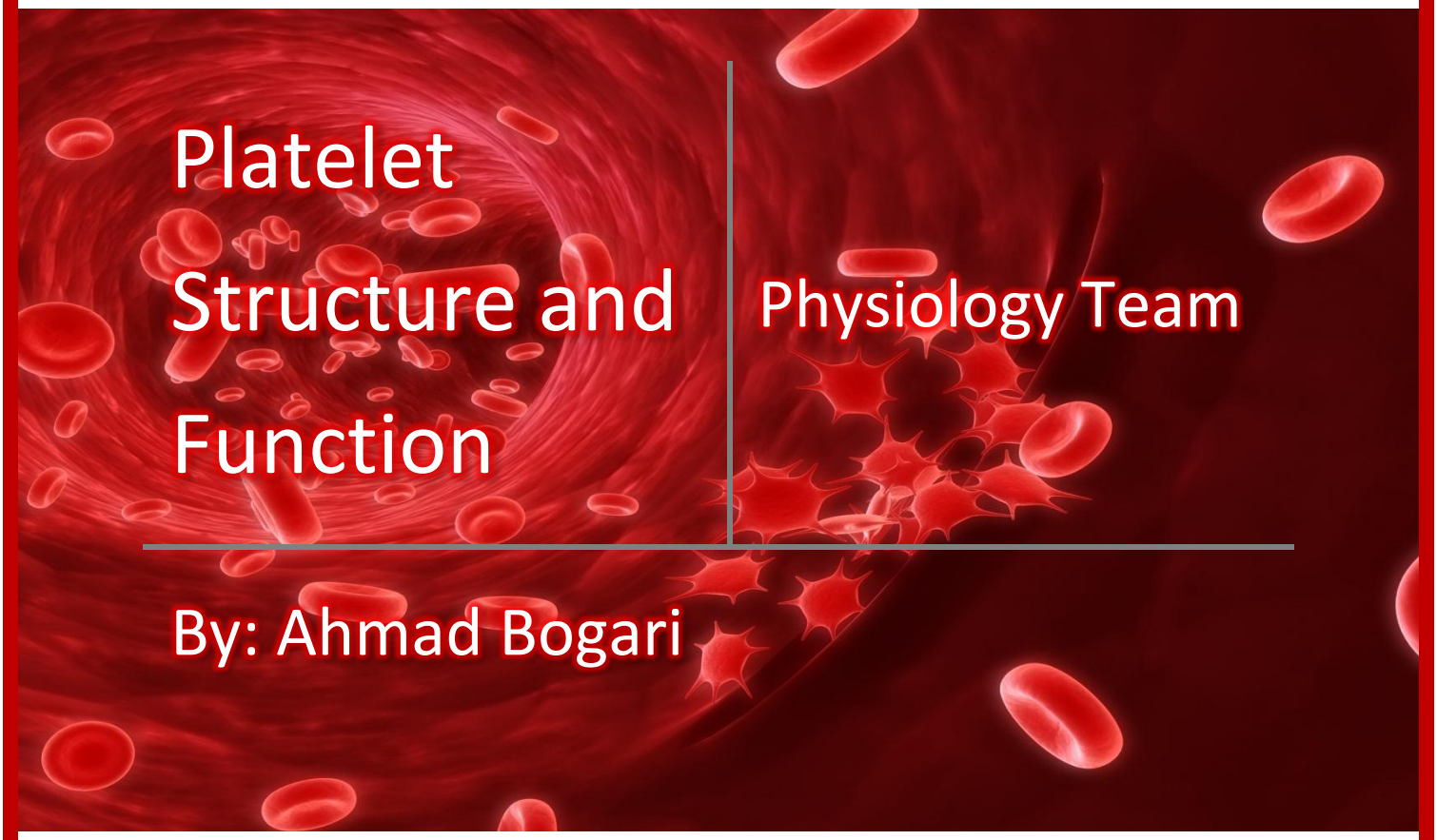

Platelet Structure and Function
Physiology Team
By: Ahmad Bogari

Notes:

- In the lecture slideshow, there were unexplained figures; I explained them here with the gray font color.
- I also added some notes which are also in gray. Go over them to have better understanding.

- **The blood is composed of:**
  - Plasma
  - Cells:
    - Platelets (Thrombocytes).
    - Red blood cells.
    - White blood cells.

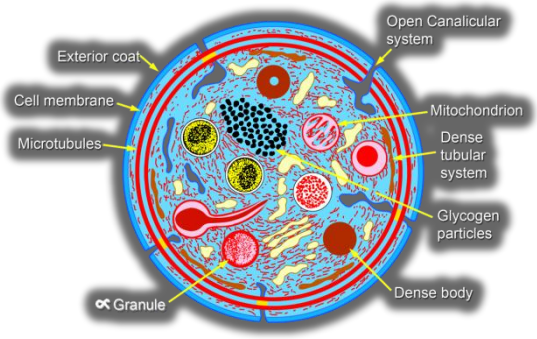
- **Site of formation**: Bone marrow.

- **Steps of formation** of platelets:
  1. Stem cell.
  2. Megakaryoblast.
  3. Promegakaryoblast.
  4. Megakaryocyte.
  5. Platelets.

- **Regulation** of thrombopoiesis by Thrombombopoietin.

- **Thrombocytes properties:**
  - Anuclear and discoid cell → Spherical when activated.
  - Size: 1.5–3.0 µm.
  - Life span: 7–10 days.
  - Sequestered in the spleen; hypersplenism may lead to low platelet counts.

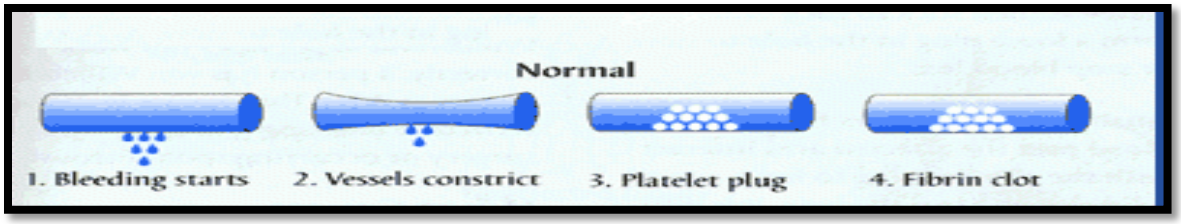
- **Thrombocytes ultrastructure:**
  - Alpha Granules:
    - Von Willebrand Factor.
    - Fibrinogen.
    - Chemokines (PF4, etc.).
    - Thrombospondin.
    - P-selectin.
  - Dense Granules:
    - ADP/ATP.
    - Calcium.
    - Serotonin.
  - Lambda granules: Similar to lysosomes and contain several hydrolytic enzymes.
  - Mitochondria.
  - Microtubules.
  - Open canalicular system.

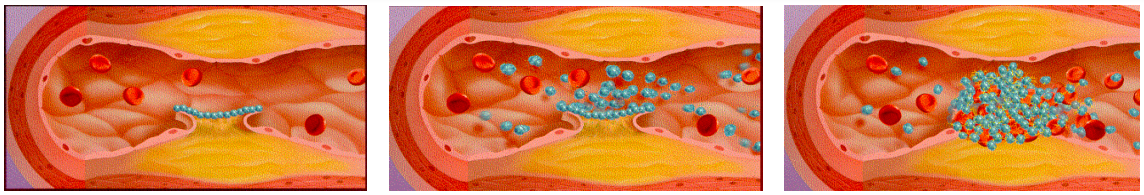


- **Platelet receptors:**
  - GP Ia, GP VI (Collagen).
  - GP Ib-IX-V (vW Factor).
  - GP IIb-IIIa (Fibrinogen, vWF).
  - TPα (TXA2).
  - P2Y12 (ADP).

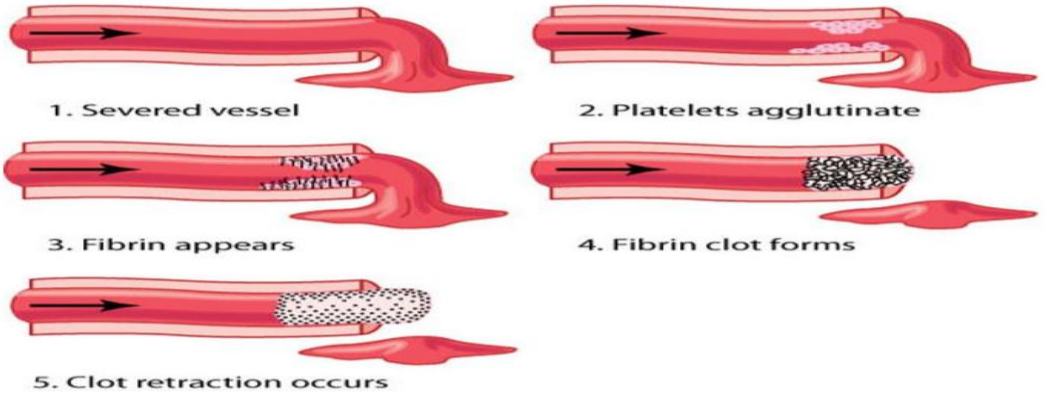
- **Hemostasis:**
  1. Vascular phase.
  2. Platelet phase.
  3. Coagulation phase.
  4. Fibrinolytic phase.

- **Platelet activation:**
  1. **Adhesion**: Fibrinogen is needed to join platelets to each other via platelet fibrinogen receptors.
  2. **Activation**.
  3. **Shape change**.
  4. **Aggregation.**
  5. **Release.**
  6. **Clot Retraction**: Myosin and actin filaments in platelets are stimulated to contract during aggregation, further reinforcing the plug and help release of granule contents.



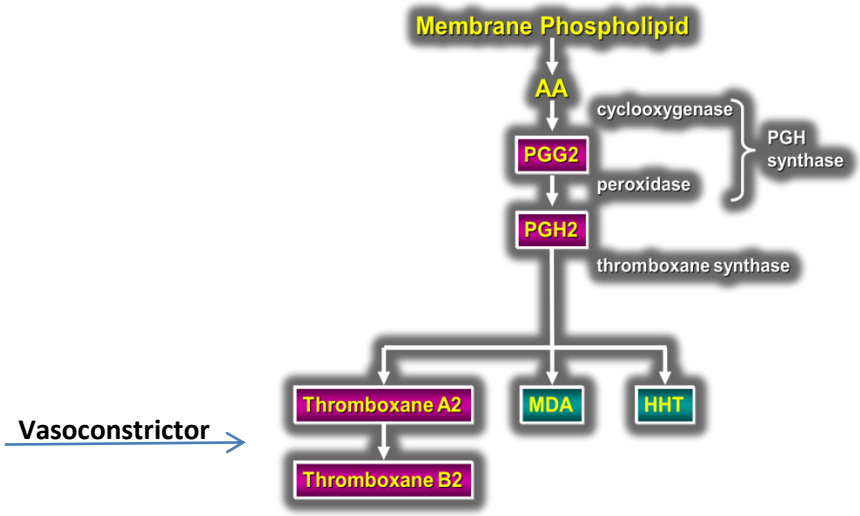


Adhesion Activation Aggregation and secretion



- Clotting takes place in three essential steps: (1) In response to rupture of the vessel or damage to the blood itself, a complex cascade of chemical reactions occurs in the blood involving more than a dozen blood coagulation factors. The net result is formation of a complex of activated substances collectively called *prothrombin activator.* (2) The prothrombin activator catalyzes conversion of *prothrombin* into *thrombin.* (3) The thrombin acts as an enzyme to convert *fibrinogen* into *fibrin fibers* that enmesh platelets, blood cells, and plasma to form the clot.
- Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall causes the smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel. The contraction results from (1) local myogenic spasm, (2) local autacoid factors from the traumatized tissues and blood platelets, and (3) nervous reflexes. The nervous reflexes are initiated by pain nerve impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues. However, even more vasoconstriction probably results from local myogenic contraction of the blood vessels initiated by direct damage to the vascular wall. And, for the smaller vessels, the platelets are responsible for much of the vasoconstriction by releasing a vasoconstrictor substance, thromboxane A2.

- In flowing blood, platelets experience tremendous shear forces and sticking to a site of injury is a major challenge. Platelet adhesion is the critical first step in hemostasis, and it requires VWF A1 domains to bind platelet GPIb. When endothelial cells are damaged, VWF binds to collagen in the exposed connective tissue. Binding to VWF slows the platelet from a mean velocity of about 1 mm/sec to about 4 µm/sec, which is slow enough to engage other receptor systems. If conditions are right, the platelet activates, spreads, binds fibrinogen, and recruits additional platelets by a similar mechanism. Even though platelets have several other receptor systems, they cannot mediate the initial adhesion event, and without VWF the process is not effective. An emerging story, developing over the past couple of years, indicates that VWF also is regulated by feedback proteolysis. Under the influence of shear stress, VWF is stretched and is cleaved by a specific protease in the blood, which cleaves the protein and limits platelet thrombus growth.



- **Activated platelets secrete**:
    1. 5HT → Vasoconstriction.
    2. Platelet phospholipid (PF3) → Clot formation.
    3. Thromboxane A2 (TXA2) is a prostaglandin formed from arachidonic acid.
        - Function:
            - Vasoconstriction.
            - Platelet aggregation.

              Note: TXA2 is inhibited by aspirin.

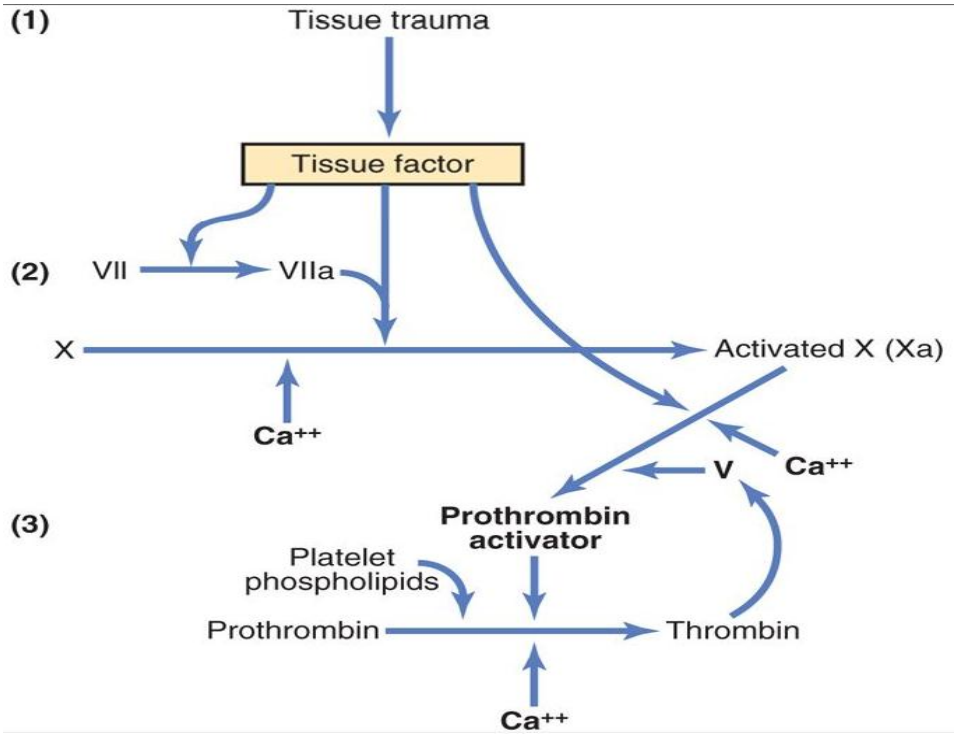
- VWF is a mobile extracellular matrix or adhesive protein.

- **Platelet haemostatic plug formation**:
  - Platelets activated by adhesion.
  - Extend projections to make contact with each other.
  - Release: Thromboxane A2, serotonin & ADP >>> activating other platelets.
  - Serotonin & thromboxane A2 are vasoconstrictors decreasing blood flow through the injured vessel.
  - ADP causes stickiness and enhances aggregation.

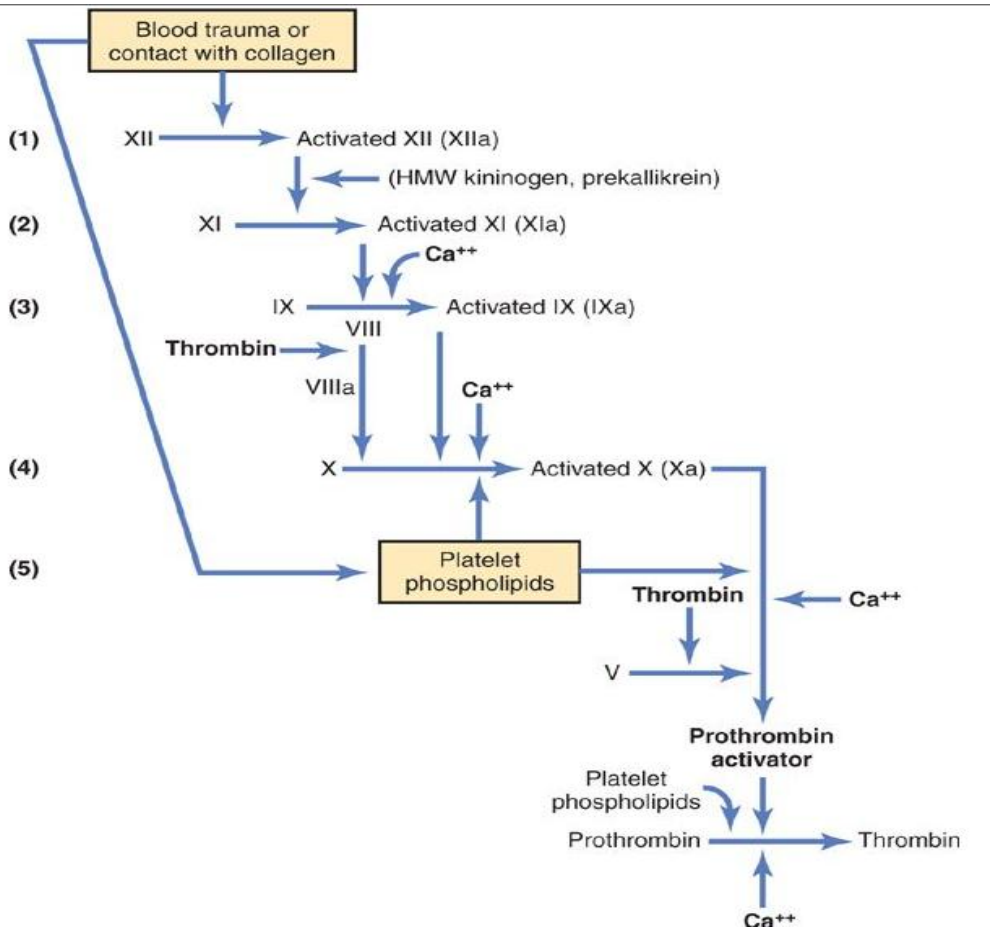
- **General functions of the platelets:**
  - Platelet plug formation.
  - Platelets and blood coagulation.
  - Positive feedback of clot formation: Once a blood clot has started to develop, it normally extends within minutes into the surrounding blood. That is, the clot itself initiates a positive feedback to promote more clotting.

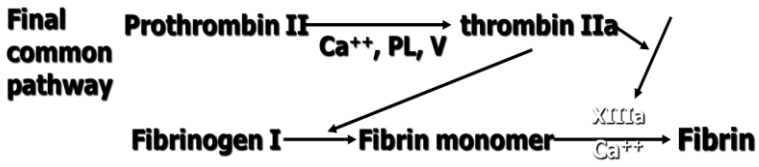
- Prothrombin activator is generally considered to be formed in two ways, although, in reality, the two ways interact constantly with each other: (1) by the extrinsic pathway that begins with trauma to the vascular wall and surrounding tissues and (2) by the intrinsic pathway that begins in the blood itself.
- In both the extrinsic and the intrinsic pathways, a series of different plasma proteins called blood-clotting factors plays a major role. Most of these proteins are inactive forms of proteolytic enzymes. When converted to the active forms, their enzymatic actions cause the successive, cascading reactions of the clotting process.
- It is clear from the schemas of the intrinsic and extrinsic systems that after blood vessels rupture, clotting occurs by both pathways simultaneously. Tissue factor initiates the extrinsic pathway, whereas contact of Factor XII and platelets with collagen in the vascular wall initiates the intrinsic pathway.
- An especially important difference between the extrinsic and intrinsic pathways is that *the extrinsic pathway* can be explosive; once initiated, its speed of completion to the final clot is limited only by the amount of tissue factor released from the traumatized tissues and by the quantities of Factors X, VII, and V in the blood. With severe tissue trauma, clotting can occur in as little as 15 seconds. The intrinsic pathway is much slower to proceed, usually requiring 1 to 6 minutes to cause clotting.

- Extrinsic pathway for initiating clotting:



- Intrinsic pathway for initiating clotting:





- **Maintenance of vascular integrity**: Adequate number and function of platelet is essential to participate optimally in haemostasis:
  - Stabilization of hemostatic plug by contributing to fibrin formation.
  - Initial arrest of bleeding by platelet plug formation.

- **Platelet activation summary:**
  - Platelets are activated when brought into contact with collagen exposed when the endothelial blood vessel lining is damaged.
  - Activated platelets release a number of different coagulation and platelet activating factors.
  - Transport of negatively charged phospholipids to the platelet surface; provide a catalytic surface for coagulation cascade to occur.
  - Platelets adhesion receptors (integrins): Platelets adhere to each other via adhesion receptors forming a hemostatic plug with fibrin.
  - Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents.
  - **GPIIb/IIIa**: the most common platelet adhesion receptor for fibrinogen and von Willebrand factor (vWF).

- **Laboratory testing of platelet function**:
  - Platelet count and shape.
  - Bleeding time.
  - Platelet Aggregation:
    - Platelet Aggregation (in PRP): Provides information on time course of platelets activation.
    - Agonists:
      - ADP.
      - Adrenaline.
      - Collagen.
      - Arachidonic acid.
      - Ristocetin.
      - Thrombin.
  - Platelet Function Analyzer.
  - Flow-cytometry.
  - Electron-microscopy.
  - Granule release products.

- **Congenital platelets disorders:**
  - Disorders of Adhesion:
    - Bernard-Soulier Syndrome.
  - Disorder of Aggregation:
    - Glanzmann thrombosthenia (No Gp IIb-IIIa Receptors which binds to Fibrinogen).
  - Disorders of Granules:
    - Grey Platelet Syndrome.
    - Storage Pool deficiency.
    - Hermansky-Pudlak syndrome.
    - Chediak-Higashi syndrome.
  - Disorders of Cytoskeleton:
    - Wiskott-Aldrich syndrome.
  - Disorders of Primary Secretion:
    - Receptor defects (TXA2, collagen ADP, epinephrine).
  - Disorders of Production:
    - Congenital amegakaryocytic thrombocytopenia.
    - MYH9 related disorders.
    - Thrombocytopenia with absent radii (TAR).
    - Paris-Trousseau/Jacobsen.