Platelets (Thrombocytes)

- **Platelets** are the smallest of the formed elements, oval or rounded, colourless, non-nucleated cellular fragments.
- They are living particles which consume O_2.
- **Their membranes contain glycoprotein coat which prevents them adhering to normal vessel wall but to attach to damaged endothelium.**
- Their main **function** is in hemostasis (control of blood loss through a damage to the vessels).

1

Platelets cont'd

- Their cytoplasm contains:
  (i) a system of microtubules and microfilaments made up of actin and myosin molecules,

  - which make it capable of contracting, and another contractile protein *thrombosthenin*.

  (ii) mitochondria and enzyme systems which synthesize ATP and ADP

2

Platelets cont'd

(iii) Golgi apparatus and smooth ER which synthesize various enzymes and stores Ca^{2+}.
The enzymes include those that can synthesize prostaglandins (PGs)

(iv) There are also many pink-staining granules containing lysosome-like enzymes, serotonin and inclusions containing glycogen.

3

Platelets cont'd

(v) important proteins among which are the fibrin stabilizing protein and a growth factor which causes vascular endothelium,

- vascular smooth muscle and fibroblasts to grow, leading to repair of damaged vessel walls.

4

Platelets cont'd

- They are formed in the fetal liver, spleen and bone marrow by disintegration of megakaryocytes,

- which are themselves derived from differentiated megakaryoblasts.

- Each megakaryocyte produces more than 1000 platelets.
- The human blood contains 300,000 (200,000-500,0000) platelets per µL of blood.

5

Platelets cont'd

- Their lifespan is 7-14 days.
- Thrombopoietin (from liver, kidneys) controls the rate of platelet production.

6

Hemostasis and Blood Coagulation

Hemostasis

- This is the mechanism of reducing escape of blood through a partial or complete defect in the wall of the blood vessels.
- It involves a complex system of processes culminating in clot formation (coagulation).

7

Mechanisms of hemostasis

The mechanisms are:

(i) Vascular spasms:

- Contraction of the vascular smooth muscles causes constriction of the damaged vessels.
- This limits blood flow to the region and thus blood loss.
- The humoral (body fluid) factor serotonin derived from platelets is primarily responsible for the vasoconstriction.

8

Mechanisms of hemostasis cont'd

ii) Platelet adhesions:

- When normal platelets make contact with the sub-endothelial collagen exposed by endothelial injury,

- they adhere to the surface and to one another using their pseudopods.

(iii) Platelet reaction:

- Following adhesion, the marginal band of microtubules contract to release the contents of the granules, which include serotonin, ADP and Ca^{2+}.
- These factors are responsible for the next crucial stage

9

Mechanisms of hemostasis cont'd

(iv) Platelet aggregation:

- ADP and a compound known as thromboxane A_2 derived from the fatty acid arachidonic acid,

- cause platelets to aggregate and accumulate at the site of the endothelial damage leading to a platelet plug.

- Thomboxane A_2 is also a powerful vasoconstrictor which enhances the effects of serotonin.

10

Blood clotting factors

- Factor I – fibrinogen
- Factor II – Prothrombin, a plasma protein
- Factor III – tissue factor, tissue thromboplastin
- Factor IV – Calcium ions, Ca2+
- Factor V – Proaccelerin, labile factor
- Factor VII – proconvertin, stable factor
- Factor VIII – Antihemophilic factor

11

Blood clotting factors cont'd

- Factor IX – Plasma thromboplastic component
- Factor X – Stuart-Prower factor
- Factor XI – Plasma thromboplastin antecedent
- Factor XII – Hageman factor
- Factor XIII- Fibrin stabilizing factor
- HMWK – Fitzgerald factor
- Prekallikrein – Fletcher factor

12

Blood coagulation mechanism

- The coagulation mechanism involves formation of a **fibrin meshwork** in and around the hemostatic (platelet) plug to seal off the vascular damage completely.
- Blood clot begins to form 15-20 sec, after severe trauma of vascular wall.
- Clotting is initiated by substances from injured vessel wall, platelets and blood proteins adhering to injured vascular wall.

13

Blood coagulation mechanism cont'd

- The compounds that promote clotting are called **pro-coagulants** and those that inhibit clotting are known as **anti-coagulants**.
- Whether blood will clot or not depends on the balance between the 2 groups.
- Anti-coagulants normally predominate and coagulation is inhibited.
- Vascular damage causes pro-coagulants to be activated, leading to development of blood clot.

14

Blood coagulation mechanism cont'd

- Coagulation of blood essentially involves the **activation of clotting factor X**,

- which in turn causes **prothrombin** to be converted into an active proteolytic enzyme, **thrombin.**

- Thrombin then converts the soluble plasma protein **fibrinogen** into an insoluble strand, **fibrin.**

15

Blood coagulation mechanism cont'd

- Fibrin will form a meshwork in the platelet plug, strengthening it and entangling blood cells to form blood clot.
- Factor X can be activated in two ways, leading to two distinct clotting mechanisms i.e. intrinsic mechanism & extrinsic mechanism.

16

Blood coagulation mechanism cont'd

Intrinsic mechanism

- This occurs in four steps.
- When blood comes into contact with a foreign surface other than the endothelial lining of

- the blood vessels, a sequence of activation of pro-enzymes is initiated, leading ultimately to clot formation.

17

Intrinsic mechanism cont'd

- In the intact vessel, contact with collagen in the vessel wall or the vascular basement membrane will activate this mechanism.
- In the laboratory, contact with glass or kaolin will initiate the mechanism.

18

Intrinsic mechanism cont'd

Step I: This contact activation causes activation of **factor XII**, in presence of **prekallikrein** and **high molecular weight kininogen** (HMWK).

- In the presence of HMWK, active factor XII (XII_a) converts **factor XI** into its active form, XI_a.

19

Intrinsic mechanism cont'd

Step II: This involves activation of factor X

- Active factor XI (XI_a) activates **factor IX** to active factor IX (IX_a), in the presence of **Ca^{2+} (factor IV)** & **active factor VIII** (VIII_a).
- The combination of IX_a, VIII_a, phospholipid from platelets and Ca^{2+} combine to form a **protein-phospholipid-Ca^{2+} complex** which then converts **factor X** into its active form, X_a.

20

Intrinsic mechanism cont'd

Step III: This involves conversion of prothrombin to thrombin.

- For this to take place, **factor X_a** forms a complex with factor **V_a**, **Ca^{2+}** and the **phospholipid.**
- It is this **complex** that catalyses **thrombin formation**

21

Intrinsic mechanism cont'd

Step IV: the final step in the intrinsic clotting mechanism involves conversion of **fibrinogen**

- into soluble **fibrin monomers** by the action of **thrombin.**

- Soluble fibrin monomers, in presence of **factor XIII_a and Ca^{2+}**, are converted into **insoluble mesh of fibrin polymer** which then seals the escape of blood.

22

Blood coagulation mechanism cont'd

The extrinsic mechanism

- The main feature of the extrinsic pathway is the activation of **factor X**,

- catalyzed by **factor VII_a** and a **tissue factor** produced from damaged surrounding tissues.

- The activated factor X will function exactly the same way as in the intrinsic pathway.

23

Blood coagulation mechanism cont'd

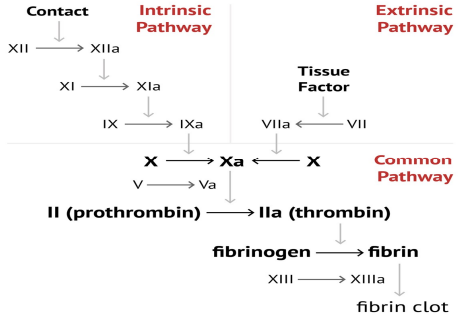
- However, the activation of factor X in the extrinsic pathway involves far fewer steps and is therefore more rapid.

- Thus the extrinsic pathway serves to improve the efficiency of the clotting mechanism so that a potentially more extensive blood loss

- involving extensive damage to surrounding tissues can be promptly controlled.

24

Coagulation cascade



25

Preventing clotting in normal blood vessels

- For blood to remain fluid in the vascular system during circulation, clotting must be held in check. Intravascular clotting is prevented by:

1. Factors of the endothelial surface:

- **Smoothness of the endothelium** which inhibits contact activation of the intrinsic clotting.
- **The glycocalyx layer**, a mucopolysaccharide lining the inner surface of the endothelium which repels the clotting factors and platelets.

26

Preventing clotting in normal blood vessels

- **Thrombomodulin**, a protein attached to the endothelium which binds thrombin to inhibit its activity.

2. Antithrombin actions of fibrin and antithrombin III:

- Fibrin fibers formed during clotting adsorb (hold) 85-90% of thrombin formed
- Antithrombin III binds the remaining thrombin

27

Preventing clotting in normal blood vessels cont'd

3. Heparin: produced by mast cells and basophils, particularly in the liver and lungs.

- In combination with anti-thrombin III, heparin is a powerful physiological anti-coagulant which removes many of the activated clotting factors from the blood.

28

Preventing clotting in normal blood vessels cont'd

4. Alpha$_2$-macroglobulin combines with the proteolytic coagulation factors causing them to be inactivated.

29

Preventing clotting in normal blood vessels cont'd

- Failure of the intravascular anti-coagulants will trigger intravascular coagulation.
- Such a blood clot is known as a thrombus.
- A thrombus will soon break away from vessel wall to form a freely floating clot known as embolus.

30

Thrombus cont'd

- The embolus may lead to blockage of the blood vessels where the clot lodges.
- This is the most frequent cause of coronary heart diseases and other vascular diseases.

31