Sheet No.

7

Physiology

Hematolymphatic System

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Platelets

Platelets are developed from a giant cell called "**megakaryocytes**" in the bone marrow; a single megakaryocyte can give rise to about **4000-6000 platelets** depend on the size of the megakaryocyte.

The differentiation time "**thrombopoiesis**" is **10 days**. Remember that RBCs and WBCs need 6-7 days for maturation in the bone marrow.

The survival time of platelets is **7-14 days** (life span is 10 days)..

The hormone which controls their formation in the bone marrow is thrombopoietin, produced mainly in the kidney and to a lesser extent in the liver.

Platelets are anucleated cells, they don't contain nuclei they are granulated bodies.

- NORMAL PLATELET COUNT (200K-400K) CELL/MICRO.L

-High count: **thrombocytosis** (bellow 150,000)
-Low count: **thrombocytopenia** (above 500,000)

There are two types of granules:

Electron dense granules:

Contain: ADP and ATP, Ca++, serotonin, histamine, and catecholamine (**adrenaline , noradrenalin, and dopamine)**

Specific alpha granules:

Contain: Acid hydrolases, growth factor, fibrinogen, factors 5 and 8, VWF (von willebrand factor), fibronectin, thromboglobulin, and platelet factor-4 (heparin antagonist).

[illegible]	Alpha-granules	Lysosomal granules
erotonin	Albumin	Cathepsin D
istamine	Fibrinogen	Cathepsin E
TP	Fibronectin	Carboxypeptidase A
DP	Vitronectin	Carboxypeptidase B
alcium	Osteonectin	Proline carboxypeptidase
lagnesium	Calcitonin	β-*N*-acetyl-D-hexosaminidas
yrophosphate	Von Willebrand Factor	β-D-glucuronidase
	Von Willebrand antigen II	β-galactosidase

In addition, platelets contain in their cytoplasm K+, Mg+, histamine, adrenaline, albumin, plasmin, antiplasmid, lipoproteins, glycoprotein, glycogen, prostaglandin, thromboxane A2.

Normally, the bone marrow contains only about **one day** reserve of platelets. Therefore, human beings are susceptible to develop

thrombocytopenia more quickly than **granulocytopenia** or **erythrocytopenia**.

Platelets produce substances that are responsible for the **integrity of blood vessels**, so in the absence of these substances, capillaries become weak and fragile, therefore RBCs leave the capillaries to the tissues which is abnormal.

Summary for major function of platelets :

1. **Platelets maintain capillaries integrity..**
2. **They play essential role in blood clotting..**
3. **They play a very important role in homostasis..**

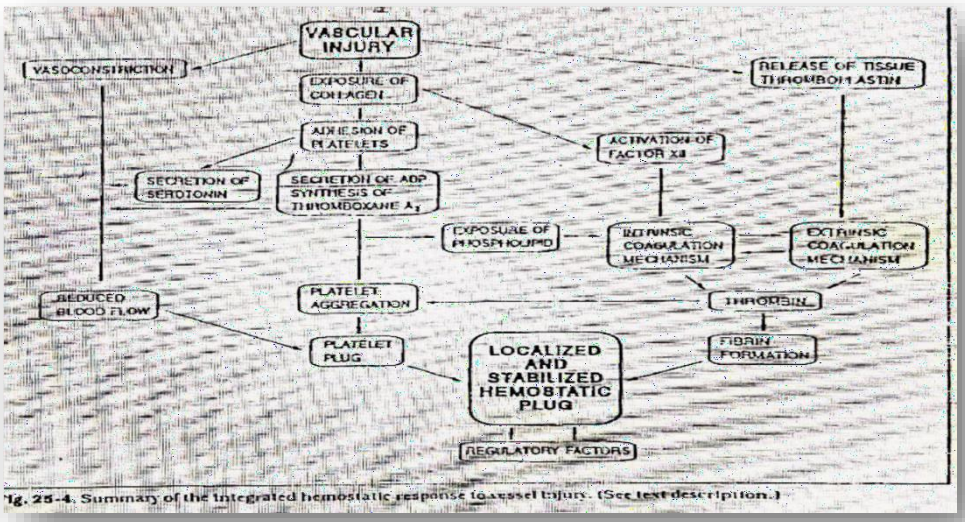


Fig. 25-4. Summary of the integrated hemostatic response to vessel injury. (See text description.)

Hemostasis

Notes:

- **Hemostasis** here is to stop blood loss through injured blood vessels .
- Platelets are **anucleated** but **they are essential for hemostasis** by their **membrane** and contents of the **granules**.

Stopping the bleeding of an injured blood vessel occurs through 3 processes:

Steps of hemostasis:

1. **Vasoconstriction** of the injured blood vessels to reduce blood flow.
2. **Platelet plug formation**
3. **Fibrin formation (clotting mechanism)**

1. Factors that cause **vasoconstriction**:

I. **Myogenic contraction** (by physical factors)
II. **Endothelin 1** (produced by the injured endothelial cells.)
III. **Adrenaline**

IV. **Serotonin** (secreted from the ruptured blood vessels)
V. **Thromboxane A2**

2. Formation of platelet plug:

A. Platelet adhesion when the blood vessels are injured collagen is exposed which is a sticky material, so together with thrombin they attract platelets to adhere to the injured surface of vessels..

Two important factors are required for platelets to adhere:

1. **Factor VIII:vWF** (found under damaged endothelium)
2. **Glycoprotien 1** on the platelet membrane

- **IF these are deficient, platelet adhesion does not ocuure properly..**

- Factor VIII (8)

Is a protein produced by epithelial cells and platelets..

It is composed of many functional parts, the most important 3 are:

i. **Factor VIII: Vwf** for adhesion .(fac.8 is carried by VWF)
ii. **Factor VIII: related Ag** for aggregation.
iii. **Factor VIII:C** for clotting and it refers to the coagulation portion of the molecule & it represents the ability of molecule.

B. Release reaction:

Adhesion causes stimulation of platelets leading to its **rapture** and release of the content of their **granules** (thrombin, ATP, ADP, TxA2, serotonin, fibrinogen, enzymes, heparin neutralizing factor & collagen)

C. Platelet aggregation

The released **collagen** and **thrombin** activate **platelet prostaglandin** synthesis leading to the formation of **thromboxane A2** that stimulate **platelet aggregation + plug formation,** also it acts as a **potent vasoconstrictor**.

At the same time of injury normal endothelium adjacent to the site of injury produce **prostacyclin** and **NO (nitric oxide)** to prevent spread of **platelet aggregation** to the adjacent normal areas (**prostacyclin** and **NO** inhibit **platelet aggregation** and **vasodilate blood vessels**).

The released **thromboxaneA2** and **ADP** cause further platelets aggregation, (**ADP** causes membrane of other platelets to **swell** encouraging their **aggregation**).

Note: aspirin delay & inhibit the production of **thromboxane A2**, However, when you take **aspirin** for **six months** you must continue it till the rest of ur life, because the body will form **dependence**. Also, if you have low platelet count you are not advised to take aspirin.

D. Platelet pro-coagulant activity

The first 3 steps occur one after another continuously, the medium becomes ready for the coagulation .This is called pro-coagulant act. Which starts after **platelets adhesion** and **release**, their membrane phospholipids (Platelet factor 3) become available for coagulation protein complex formation.This phospholipid surface forms and ideal template for the crucial concentration and orientation pf these proteins for normal coagulation cascade reaction.

E. Platelet fusion

- After **vasoconstriction**, **platelets plug formation** and **clotting**, injury is closed. Bleeding is stopped because of platelet plug formation..
- High concentrations of **ADP** & **thrombasthenin (an important component of the clot retraction sys. google) as well as the enzymes released during the reaction** contribute to **an irreversible fusion** of platelets aggregated at the site of vascular injury.
- **Thrombin** also encourages fusion of platelets and **fibrin** formation reinforces the stability of the evolving platelet plug.

3. Clotting factors

Clotting mechanism is activated by the release of tissue **thromboplastin**, activation of **factor XII** and release of **platelet phospholipids (platelet factor 3).** When thromboplastins are produced they encourage the clotting mechanism which needs clotting factors produced in the liver

- ✓ Almost all factors are produced in the **liver**, so any **liver** disease will affect clotting.

Table 12.3 The major components of the coagulation pathway (enzymes, protein cofactors, and substrates) involved in fibrin formation and fibrin degradation.

Component	Synonym	Site of synthesis
Fibrinogen	Factor I	Liver
Prothrombin	Factor II	Liver*
Thrombin		Plasma
Tissue factor	Thromboplastin	Vascular endothelium
Factor V		Vascular endothelium
Factor VII		Liver*
Factor VIII	Antihemophilic factor	Vascular endothelium
Factor IX	Christmas factor	Liver*
Factor X	Stuart factor	Liver*
Factor XI	Plasma thromboplastin antecedent	Liver
Factor XII	Hageman factor	Liver
Factor XIII	Fibrin stabilizing factor	Liver
von Willebrand factor	vWF	Vascular endothelium
Prekallikrein	PK, Fletcher factor	Liver
High-molecular-weight kininogen	HK, HMWK	Liver
Protein C		Liver*
Protein S		Liver*
Thrombomodulin	TM	Vascular endothelium
Plasminogen		Liver
Tissue-type plasminogen activator	t-PA	Liver
Urokinase-type plasminogen activator	uPA, prourokinase	Unknown

-Factors that require **vitamin K** for their synthesis (vitamin –K dependent factors) are **factor II**, **factor VII**, **factor IX**, **factor X** (rem: (10=1)972), **protein S** & **protein C**.

- Factors and their synonyms are **required**!

-When vascular injury occur, these factors are released to encourage the coagulation process.

Clotting pathways:

1. Intrinsic pathway
2. Extrinsic pathway
3. Common pathway

➢ Intrinsic pathway :

1. Activated **factor XIIa** , **prekallikrien** and **HMW-K** (**high molecular weight kininogen**) after the exposure of these to the foreign surfaces ,these 3 elements activate **factor XI**.
2. Platelets can directly activate **factor XI**(which is also activated by **factor XII)**
   - Therefore, people with the deficiency of factor XII ,prekallikrein and HMWK, they don't complain from serious bleeding problems, while people with deficiency of factor XI suffer from moderate-sever bleeding.

3. Then Factor XIa activate factor IX in the presence of calcium.
4. Factor IXa with factor VIIIa , calcium and phospholipids form a complex called **Tenase.**
5. **Tenase** activate **factor X.**

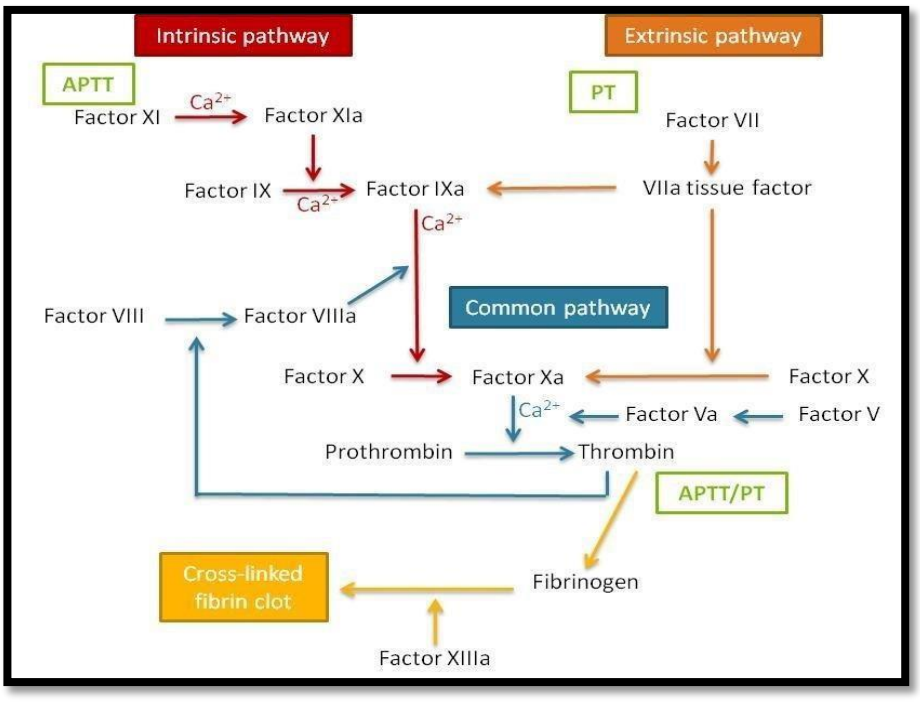
➢ Extrinsic pathway:

1. Starts by the release of tissue **thromboplastin (which contains phospholipids)**, **factor VII** and **calcium** form a **complex**.
2. This **complex** activate **factor X**.
    - These two pathways function at the same time and both activate **factor X** at the end.

➢ Common pathway:

This pathway begins after activation of **factor X**

1. Activated **factor Xa**, factor **Va**, **phospholipids** and **calcium** form an **enzyme** called **thrombokinase**, it activates **prothrombin** to form **thrombin**.
2. **Thrombin** activates **fibrinogen** to form **fibrin threads**, but they **are=**



=unstable.

3. **Fibrin** begin to polymerize but it's fragile and soluble **(unstable)** at the beginning.

4. **Factor XIII (fibrin stabilizing factor)** in the presence of **thrombin** and **calcium** stabilize **the fibrin that become insoluble.**

- All the components of the **intrinsic pathway** are present in the **plasma** that is why it is so called.
- This pathway (intrinsic) is usually **slow**, **weak** and takes about **6 minutes**, but it is **long–acting** and **more important**!
- **The extrinsic pathway** which occurs because of the tissue damage is **fast** and **powerful**, it takes about **16 seconds!**

➢ Function of thrombin:

The main function of **thrombin** is the activation of **fibrinogen**, to form **fibrin threads.** There are also. There are also other factors:

1. Activation of fibrinogen.
2. Activation of factors V, VIII and (XIII (that stabilizes the fibrin threads)).
3. Activation of platelets.
4. Activation of **protein c** through binding to **thrombomodulin**.

If we eliminate calcium from blood, it won't clot!!

- **Calcium** ions are required for each step in the coagulation process, except for **the first two** reactions in the **intrinsic pathway**. Even if we eliminate these two steps from the reaction **it will continue**.
- **EDTA** is used for **chelating** and **removal of calcium** to prevent blood clotting.

➢ Function of calcium:

1. Activate **enzymes**
2. Activation of **platelets**, also it is present within them.
3. Activate secretion of the **granules** especially **alpha granules**.
4. Activate contraction of **actin & myosin** in the membrane.

- **The main source of calcium for the coagulation mechanism is liver.**

➢ Normal fluidity of the blood:

If the blood clots very easily this will result in **thrombosis**, and if it takes too long to clot the result will be **hemorrhage**, therefore we need the blood to flow **normally**.

➢ Factors that maintain normal fluidity of the blood:

1. Presence of **heparin** in the plasma (produced in basophils), **the most imp. one**.
2. The main clotting factors, **prothrombin** and **fibrinogen** exist in plasma in an **inactive** from, and part of them are removed by **the portal circulation** of the liver, so their conc. will be reduced.
3. **Endothelial lining** of vessel is **smooth** and **negatively** charged, so it repels platelet adhesion.
4. **Antithrombin III:** inhibits the action of **thrombin** as well as the activated factors **IXa**, **Xa**, **XIa** and **XIIa**.
5. **Thrombin** bind to **thrombomodulin**, leading to activation of **protein s** and **protein c**, which in the presence of **calcium** and **phospholipids** inactivate **factors V, VIII**.

➢ Protein **c** & **s** require **vitamin K.**

6. **A2 macroglobulin** & **A1 antitrypsin**, also contribute to the **anti-thrombin** effect of plasma & **fibrinolytic** system.
7. **Fibrinolytic system.**

➢ In every person, there are **minor clotting** that dissolve immediately which results in **fibrin** & **fibrinogen** degradation products that work as **anti-coagulant**. It inhibits the **fibrin threads** and **platelets aggregation**.

➢ Fibrinolytic system (fibrinolysis):

- The **essential** step in this system is the production of **plasmin**
- The plasma proteins contain a euglobulin called **plasminogen** (profibrinolysin) ,that when activated becomes a substance called **plasmin** (fibrinolysin).017
- **Plasmin** is a **proteolytic** enzyme that lysis **fibrin** fibers, **fibrinogen**, and **activated factors V**, **factor VIII**, **prothrombin** and **factor XII**.
- **Fibrin** and **fibrinogen degradation products** act as **anticoagulants;** they **inhibit** the **fibrin threads** and **the platelet aggregation.**
  - ✓ So fibrolytic system or fibrolysis means the production of **plasmin**.
  - ✓ Fibrinolysis like **coagulation**, it's a normal **hemostatic** response to a vascular injury

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➢ Plasminogen activators:

1. Exogenous activators:

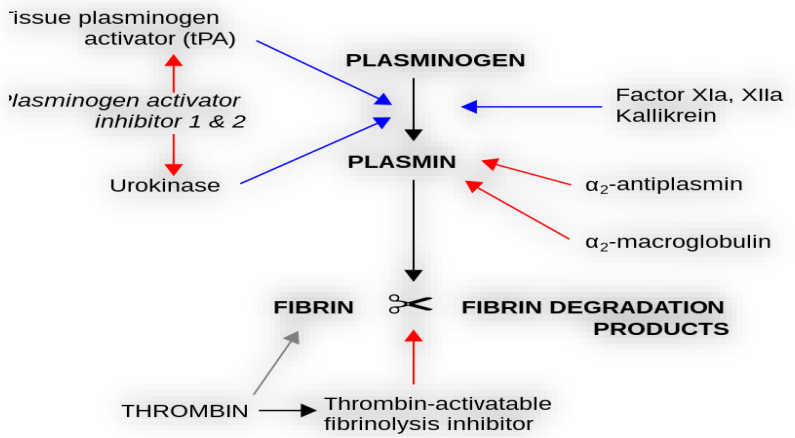
- **Urokinase**: presents in the plasma and urine
- **Streptokinase**: from streptococcus bacteria.

2. Endogenous activators:

- **Tissue plasminogen activator**: produced by endothelial cells.
- **Contact phase of coagulation**

NOTE: Tissue **plasminogen** activator and **streptokinase** are **lifesaving** injection, because they **lyse** the clot (thrombus) within seconds.

- ✓ On the other hand, there is a substances that inhibit plasmin → **Alpha2 antiplasmin controls its normal production.**



✓ **Note**: both factor 5 &8 have nothing to do in the absence of fibrin or fibrinogen..

➢ Clot Retraction and Expression of Serum:

- The clot retraction time measures the ability of the blood clot to retract.
- If we take a blood in a tube and leave it for more than one hour, clot retracts (partially or fully retraction).It shrinks to about 50% of the original size. In normal blood , the clot retracts as follows:

✓ After 2 hours, there is partial retraction of the clot.
✓ After 24 hours, there is complete retraction of the clot.

- If we remove the clot, the remaining is serum that doesn't contain clotting factors, so it doesn't clot while the plasma clots.
- When the platelet count us decreased, the clot retraction time is increased.
- The clot retraction time is used in the diagnosis of hemorrhagic diseases

➢ Two factors which play a vital role in clot retraction:

1. **Platelets**: when there is no normal platelet count no clot retraction would result.
2. **Calcium** (actin and **myosin** contraction) + no coagulation of plasma without calcium!

➢ Thrombosis & embolism

- Sometimes unwanted clotting is formed in the blood vessels, which called **thrombosis**, the clot itself is **thrombus/thrombi**.
- This clot may dissolve (minor clotting dissolve immediately).
- The clot may be removed from its attachment (If they are not dissolved) and carried with blood, this circulating clot is called embolus / emboli the condition is called embolism.
- Embolus may be **clot**, **bubble** of **air**, and **fat** from **broken bone** or **piece of debris**.
- Emboli can be swept by the blood through the heart and pulmonary artery to lodge in and obstruct a small artery in the lung.
- **Thrombi** in arteries **are more dangerous** than in the vein, especially when the artery is one that carries blood to the vital regions such as the brain or heart muscle.
- **Atherosclerosis** or **Arteriosclerosis** (condition related to embolism or thrombosis):
  - ✓ These are the conditions underlying most heart attacks.
    - ❖ **Atherosclerosis**: accumulation of **lipids** in blood vessels, can be as a result of **DM**.
    - ❖ **Arteriosclerosis**: related to **loss of elasticity** & **flexibility** of the walls of arteries.

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➢ Causes of thrombosis in man:

- **Injury to blood vessel** by trauma, or application of an irritating substance, which activate the **intrinsic** or **extrinsic** coagulation rout.
- **Infection**: in the vicinity of cellulitis and the abscesses the endothelium becomes injured through inflammatory responses, these induce **platelet adhesion** to injured endothelium, with **ADP** release to increase the platelet aggregation.
- **Slowing of the blood stream**: After major surgery or childbirth, there is an increased risk of developing **thrombosis** and **embolism**. This may be due to the fact that the flow of blood in veins becomes sluggish, that results in platelet deposition and clotting.
- **Changes in the blood composition**: After operation or childbirth, both the number of platelets and the level of fibrinogen are increased, an important factor leading to **thrombosis** is probably an alteration in platelet stickiness, associated with alteration in the endothelium and slowing g of blood flow.