

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

### Platelets :

1. Are developed from the giant cells "**Megakaryocytes**" in the bone marrow.
2. Generally we can say "**platelets are granules** ", they don't contain nucleus.
3. Differentiation time of platelets is **10 days** .

Q /In erythropoiesis , the differentiation time is **6 days** , in leucopoiesis also it is **6 days** , so what's the difference between erythropoiesis and leucopoiesis ??

white blood cells when they are produced , they remain in the bone marrow for a longer duration .

4. the hormone which regulates thrombopoiesis is called **thrombopoietin** ; produced by the kidney and little from the liver .
5. Survival time is **7-14 days** ( almost 10 days ) .
6. Normal count is **150,000 to 450,000** .

7. low count is called **thrombocytopenia** , high count is called **thrombocytosis** .

8. the main function of platelets is in **hemostasis** and in **clotting** .

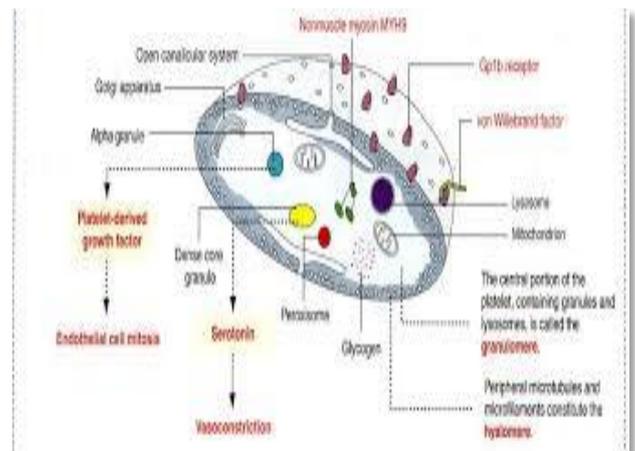
9.platelets as we mentioned above are **granulated bodies** , they contain 2 types of granules :

a. Electron dense granules , which contain ( **nucleotides (ADP)** , **serotonin** , **Ca<sup>++</sup>** and **chatecholamines ( adrenaline )** ).

b. Specific alpha-granules , contain ( **acid hydrolases** ,**growth factor** ,**fibrinogen** ,**Factor V** ,**Factor VIII:VWF** ( von Willebrand factor ) ,**fibronectin** , **thromboglobulin** and **PF4** ( heparin antagonist)

10. The following chemicals also are found inside the platelets, either in the granules or inside the cells (**k<sup>+</sup>**, **Mg<sup>++</sup>**, **Histamine**, **Adrenaline**, **Albumin**, **Antiplasmins**, **Lipoproteins**, **prostaglandins** & **thromboxanes**) .

11. In the cytoplasm of platelets , there are factors that are responsible for the **integrity** of blood vessels, if these factors are absent or there is a problem in the count of platelets , the health of blood vessels will be affected ; RBC's will leave blood vessels into tissues , and this is **abnormal**.



Remember that 75% of the cells in the bone marrow belong to **WBC's** , and 25% belong to **RBC's** , very little to the platelets  $\implies$  therefore , human beings are susceptible to develop **thrombocytopenia** more than to develop **granulocytopenia** or **erythrocytopenia**.

Some people whom their origin is African (blacks in Europe and America), have low white blood cells count.

This is known as **genetic Leukopenia**.

Also there is what's known as **environmental erythrocytopenia** , in which RBC count is low.

As we mentioned before , platelets maintain capillary integrity , so when injury of blood vessel occur , hemostasis takes place to prevent blood loss.

**Hemostasis : stopping the loss of the blood from the injured vessel .**

In hemostasis , 3 reactions take place to prevent the blood loss:

**1.** Vasoconstriction of blood vessel as well as neighboring endothelial cells  $\implies$  for reducing **blood** flow .

Q/What are the factors that play a role in vasoconstriction ?

**A. Physical factors ( reflex ).**

**B. Secretion of serotonin.**

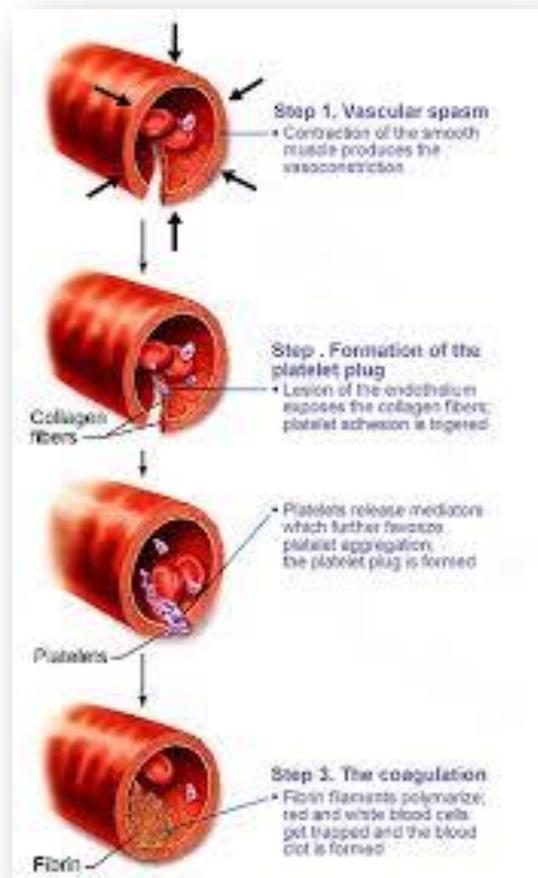
**C. Release of thromboxane A<sub>2</sub>( from platelets) , which is a vasoconstrictor.**

**D. Adrenaline**

**E. Endothelin 1 ;**from the injured endothelial cells.

**2.** Platelet plug formation :

After a blood vessel is injured , collagen is exposed and attracts the platelets more than any other element of the blood .



**Steps of plug formation ( in brief ):**

- a. Platelet adhesion** ; platelets adhere to the surface of the injured blood vessel .
- b. The release reaction**; when platelets adhere , they will be stimulated and release the contents ,means that the chemicals inside the granules as well as inside the cell are released.
- c. Platelet aggregation** : These released chemicals will stimulate the aggregation of the platelets ( accumulation of platelets above each other).

During platelet aggregation and release reaction, **platelet factor 3** is produced, which is a phospholipid chemical , this factor prepares the medium for coagulation mechanisms and this is called

**d. Platelet Procoagulant Activity**

- e. Platelet fusion** : with adhesions more and more and coagulations , the fibrin chains are formed, and at the end the injury is fused with the platelets fused .

***here are important details for the previous steps :*****1. platelet adhesion :**

Two very important factors are involved —→ **a.** factor VIII : VWF , originating during the injury, and need other parts of factor VIII ( mentioned in the box below ).

Deficiency of any of these ( Factor VIII parts ), will affect and disturb the process of adhesion

—→ **b.** glycoprotein -1 on the platelet surface membrane

Note that we are talking about a part of factor VIII, which is "VWF" ; that means there are another parts of factor VIII.

For example: **factor VIII – related antigen**, for aggregation

And factor **VIII:C**, The coagulant (for blocking)

**So , the presence of factor VIII parts and glycoprotein on the surface is essential for the normal adhesion of platelets .**

**2. The release reaction ;**

- a. Collagen exposure or thrombin action results in the release of ADP, serotonin, fibrinogen, lysosomal enzymes and heparin neutralizing factor

b. collagen and thrombin raise the production of two substances at the same time ; one for the aggregation and the second is against aggregation .

**Thromboxane A<sub>2</sub> ———> stimulate platelet aggregation and also has potent vasoconstrictive activity.**

**Prostacyclin (PGI<sub>2</sub>) ———> inhibits platelet aggregation and is a vasodilator**

Another substance is also produced along with prostacyclin ; nitric oxide (NO) , and is produced from endothelial cells.

If there is a deficiency in the production of thromboxane A<sub>2</sub> , the aggregation will not occur properly.

\* **Aspirin role as anti- platelets , many people ( more than 90% of people in Europe and America) take it as preventive medicine , because it decreases the production of TxA<sub>2</sub> and subsequent decrease in coagulation .**

**There are problems in ingestion of aspirin in some people ; old people**

If you take aspirin for more than one year, then you can't cut it , if you do so then abnormality occurs ( bleeding occurs )

Also aspirin can produce stomachache , ulcer ....etc.

### 3. platelet aggregation :

Released ADP and thromboxane A<sub>2</sub> cause additional platelets to aggregate above each other.

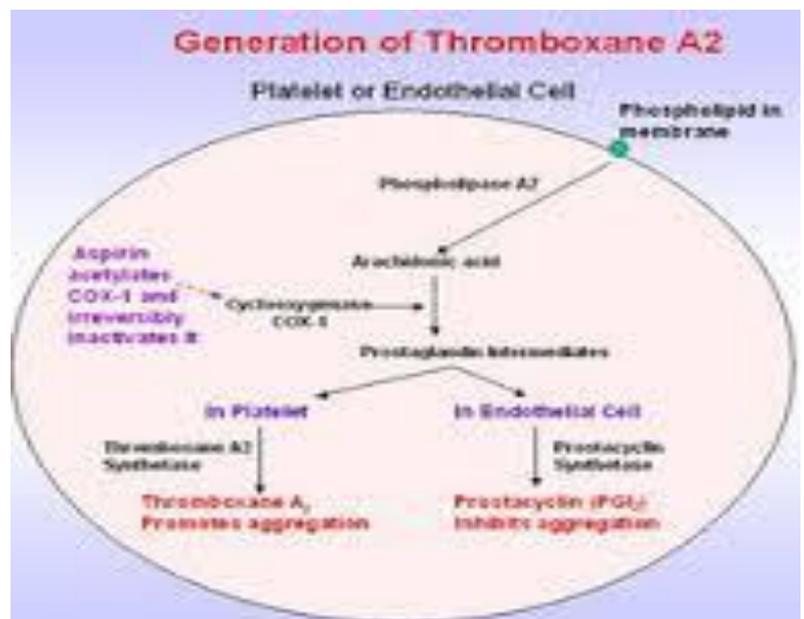
ADP causes the platelets to swell and encourages the platelet membranes of adjacent platelets to adhere together.

### 4. platelet procoagulant activity :

During aggregation , platelet factor 3 is produced , this factor prepare proper medium for coagulation .

### 5.platelet fusion :

High concentrations of ADP, the enzymes released in the membrane and thrombasthenin 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.

**Which one of these plays more important role in case of injury, ( platelet coagulation , clotting or fibrin )??**

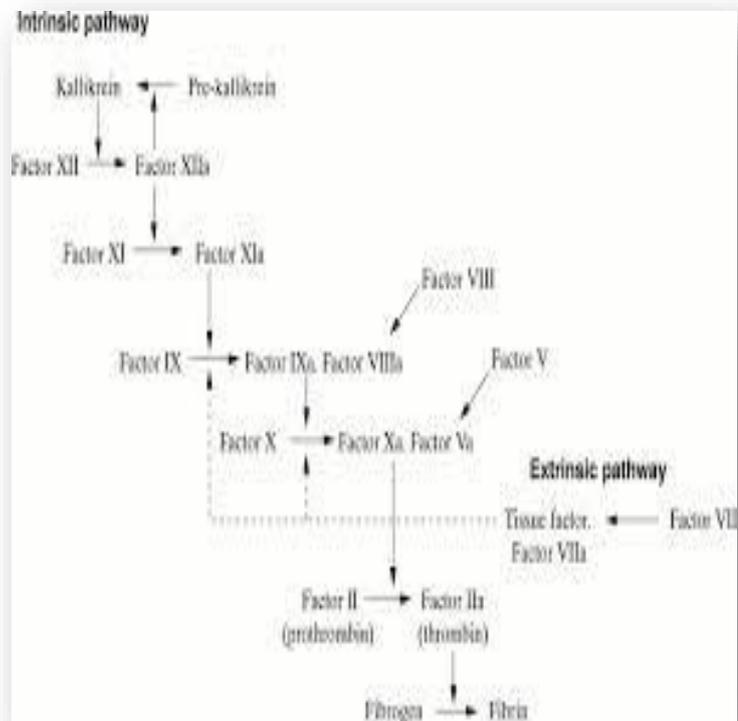
**It depends on the degree of the vascular injury .**

*Summary of the process from vascular injury till fibrin formation; the actions occur in hemostasis:*

1. During vascular injury, release of **tissue thromboplastin** takes place, this activates extrinsic coagulation mechanism.

2. While the exposure to foreign surface, such as collagen, activates factor XII and this activates intrinsic coagulation mechanism.

Both intrinsic and extrinsic pathway , at the end, lead to the formation of **thrombin** , which in turn leads to fibrin formation .



### Coagulating factors:

Almost all the clotting factors are produced in the liver .

Factor II, factor VII, factor IX and factor X are **vitamin K-dependant factors**.

**Intrinsic pathway;** begins with the exposure of factor XII to the foreign surface ( negatively charged ) and it's activated .

2. Activated **factor XII** along with two other factors ; **HMW-K** ( high molecular weight –kininogen ) and **Prekallikrein** , play role in activation of factor **XI**

Role of **HMW -K** ; is to bind prekallikerin and factor XI to keep them close to factor XII ( keep them close to the surface of the injury ) .

**The deficiency of these 3 factors don't produce serious problems , because platelets are able to activate factor XI without them**

**However , the deficiency of factor XI do produce serious problems .**

3. Activated Factor **XI** activates Factor **IX** in the presence of calcium.

4. Activated factor **IX** + Factor VIII + phospholipids + Calcium  $\longrightarrow$  form a complex that activates factor **X**

"**Intrinsic**; means that all the component are present in blood "

This pathway is slow and weak ( need minutes ) , but long lasting and more important

**Extrinsic pathway;**

1. begins with the production of tissue factor (thromboplastin) , after the injury .

2. Tissue thromboplastin + factor VII + Calcium $\longrightarrow$  form a complex that activates factor **X**.

This pathway is very fast , occurs post to the tissue damage ( occur within seconds )

**Common pathway after factor X activation;**

1. activated factor X + Factor V + phospholipids + calcium  $\longrightarrow$  form a complex called thrombokinase ; which catalyzes the conversion of prothrombin to thrombin .

2. thrombin activates fibrinogen to form fibrin

3. fibrin polymer is insoluble and unstable , need to be stabilized by the activation of **factor XIII** in the presence of thrombin and calcium.

4. At the end insoluble stable fibrin is produced .

**Note that if we remove calcium from the blood , blood don't coagulate** , what is the most important thing that removes or eliminate calcium from blood ? citrate but in labs the most important is **amylase** ( not sure about the enzyme )

Calcium is present in all steps of blood coagulation except the first 2 steps of the intrinsic pathway .

What do you think most important in vivo , extrinsic or intrinsic pathway , remember in vivo , coagulation is abnormal ; normally no coagulation ?

Extrinsic are more important ; when there's infection or inflammation , it attracts monocytes and together with inflammatory process ( inflammation ), they produce the tissue factor.

The doctor said first intrinsic is more important , then said that it's extrinsic :O

### **Additional points on the clotting system**

1. both intrinsic and extrinsic pathways are necessary for normal hemostasis
2. both pathways are activated when blood leaves the blood vessels for the tissues

\*Question asked by the doctor at the end of the lecture , does the plasma coagulate ?

Yes , because all the coagulation factors are present in plasma , and when we do centrifugation to the blood , plasma along with coagulation factors remain suspended and do coagulation.

### **Thrombin functions;**

1. activation of factor VIII , V, XIII, and fibrinogen
2. activation of platelets
3. activation of protein C ; play role in anticoagulation processes.

### **Calcium functions ;**

1. phospholipase activation
2. secretion of granules
3. contraction of Actomyosin

Finished ☺

The doctor said contradicts in some points , I am sorry for any mistake

Alaa shqeirah

