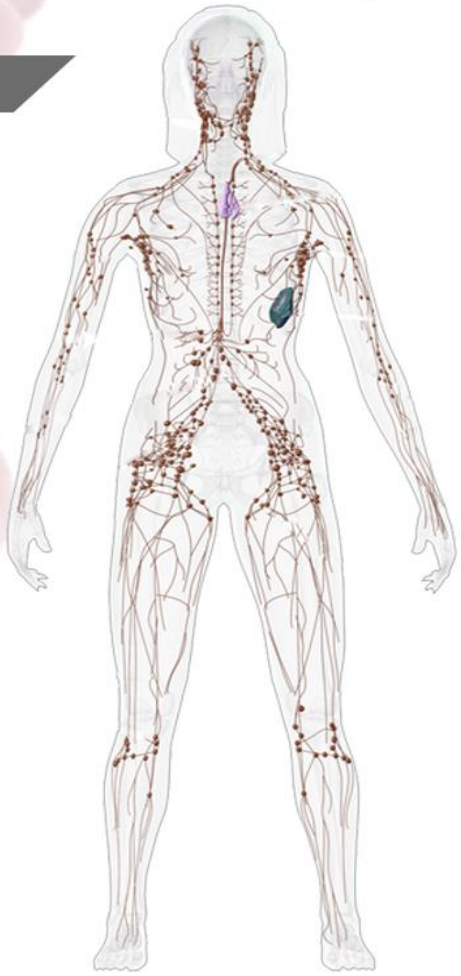
Sheet 9

Hematology and Lymphatic system

Subject | Physiology



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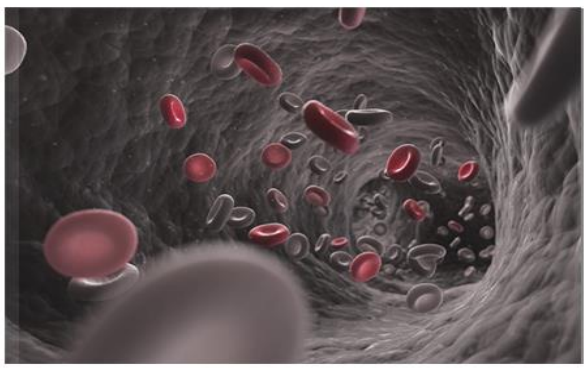

Platelets

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.

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 anucleate cells, they don't contain nuclei they are granulated body.

Normal platelet Count (200k-400k)

o High count: thrombocytosis

o Low count: thrombocytopenia

Note: above 400k platelets in normal individual are very little but bellow 200k are relatively high.

Hemostasis

Note: Hemostasis is to stop blood loss through injured blood vessels

Platelets are anucleate but they are essential for hemostasis by their membrane and contents of the granules.

There are two types of granules:

1. **Electron dense granules:**

   Contain: ADP and ATP, Ca++, serotonin, histamine, and catecholamine.

2. **Specific alpha granules:**
   Contain: Acid hydrolases, growth factor, fibrinogen, factors 5 and 8, fibronectin, beta-thromboglobulin, and platelet factor-4 (a heparin antagonist).

In addition, platelets contain in their cytoplasm K+, Mg+, histamine, adrenaline, albumin, plasmin, 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.

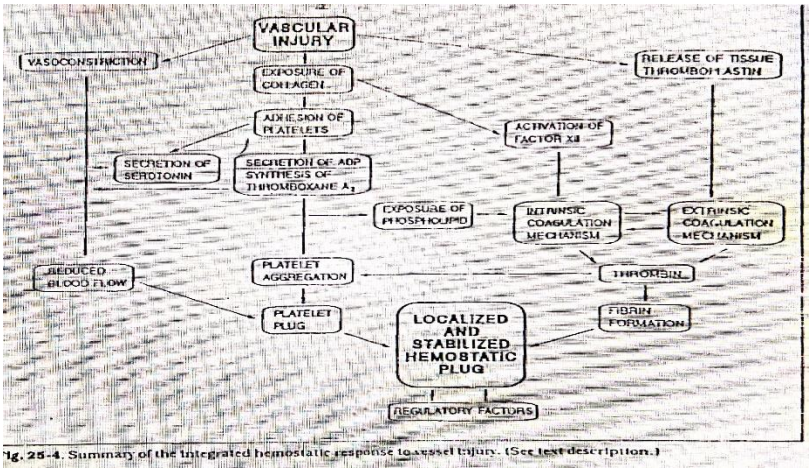

Fig. 25-4. Summary of the integrated hemostatic response to vessel injury. (See text description.)

Steps of hemostasis:

1. **Vasoconstriction of the injured blood vessels**

Factors that cause vasoconstriction:

- Myogenic contraction by physical factors
- Endothelin 1
- Adrenaline
- Serotonin
- Thromboxane A2

Vasoconstriction reduce blood flow through injured vessel.

2. **Formation of platelet plug**
   A. **Platelet adhesion**

when the injured surface become sticky because of the collagen platelets adhesion to the injured surface.

Two important factors are required for adhesion:

1. Factor VIII:vWF
2. Glycoprotien1

Note: Factor VIII is produced from epithelial cells and platelets, also, it is composed of many parts, the most important are:

i. Factor VIII:Vwf for adhesion
ii. Factor VIII: Ag for aggregation
iii. Factor VIII:C for clotting

B. Release reaction

Adhesion causes stimulation of platelets leading to its rapture and release of the content of their granules.

C. Platelet aggregation

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

At the same time of injury normal endothelium adjacent to the site of injury produce **prostacyclin** and **NO** 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 the production of thromboxane A2, However, when you take aspirin for six months you must continue because the body will form dependence. Also, if you have low platelet count you are not advised to take aspirin.

D. Platelet procoagulant activity

Platelets rupture cause release of its membrane phospholipids (platelet factor 3) that prepare proper media for coagulation (procoagulant activity).

E. Platelet fusion

After vasoconstriction, platelets plug formation and clotting injury is closed.

Note: wasn't mentioned by the doctor, High concentrations of **ADP** & **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.

3. **Formation of blood clot (coagulation)**

Clotting mechanism is activated by the release of tissue thromboplastin, activation of factor XII and release of platelet phospholipids (platelet factor 3).

Clotting factors

Factor	Name (synonyms)	Site of formation
I	Fibrinogen	Liver
II[a]	Prothrombin	Liver
III	Tissue thromboplastins	Tissue cells (membrane protein)
IV	Calcium ions	
V[b]	Labile factor	Mainly liver
VII[a]	Stable factor	Liver
VIII[b]	Anti-haemophiliac globulin A (AHG)	Platelets, RES endothelial cells, liver
vWF	von Willebrand's factor	Endothelial cells, platelets
IX[a]	Anti-haemophiliac globulin B (Christmas factor)	Liver
X[a]	Stuart factor	Liver
XI	Plasma thromboplastin antecedant factor (PTA)	Liver
XII	Hageman factor	Liver
XIII	Fibrin stabilizing factor	Liver
TF3	Platelet factor 3	Platelets

Note
[a] vitamin K-dependent [b] pro-cofactors

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

Factors that require vitamin K for their synthesis (vitamin –K dependent factors) are factor II, factor VII, factor IX, factor X, protein S & protein C.

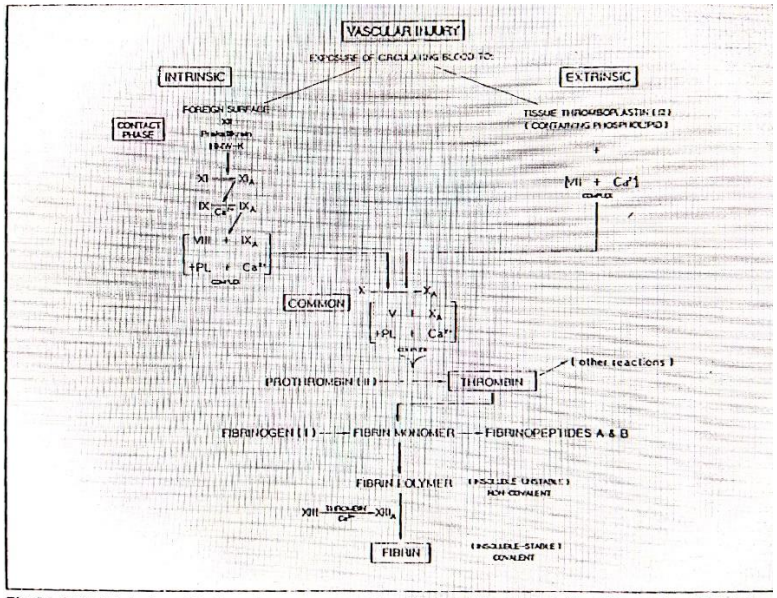

Fig. 24-5. The intrinsic, extrinsic, and common enzymatic pathways of blood coagulation. (See text for detailed description.) (*HMW-K* = high-molecular-weight kininogen; *PL* = phospholipid.)

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

Extrinsic pathway

1. Tissue thromboplastin, factor VII and calcium form a complex.
2. This complex activate factor X.

Common pathway

This pathway begins after activation of factor X

1. Factor Xa , factor Va , calcium and phospholipids form a complex called **thrombokinase**.

2. **Thrombokinase** activate prothrombin to form **thrombin**.

3. **Thrombin** activate **fibrinogen** to form **fibrin**.

4. **Fibrin** begin to polymerize but its fragile and soluble **(unstable)** at the beginning.

5**. Factor XIII** (**Fibrin stabilizing factor**), **calcium** and **thrombin** stabilize **fibrin** threads that become insoluble.

Intrinsic pathway is slow, occurring in 6 minutes and weak, but its long lasting and more efficient.

Intrinsic pathway is named so because all its components are in the blood.

Extrinsic pathway is fast, occurring in 16 seconds and powerful.

The extrinsic and intrinsic pathways function together at the same time.

Factor XI could be activated directly by platelets, so a deficiency in factor XII, kallikrien, HMW-k will not cause problems (bleeding), but deficiency in factor XI cause severe problems.

Extrinsic more important than intrinsic.

Function of thrombin:

- Activation of fibrinogen.
- Activation of factors V, VIII and XIII.
- Activation of platelets.
- Activation of protein C

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

* calcium ions are required for each step 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- Activate granules
3- Activate 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.

Factors that maintain normal fluidity of the blood:

1. Presence of heparin in the plasma (produced in basophils).

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.

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 lXa, Xa, Xla and Xlla.

5. Thrombin bind to thrombomodulin, leading to activation of protein s and protein c, that in the presence of calcium and phospholipids inactivate factors V, VIII.

6. **a2 macroglobulin** & **a1 antitrypsin**, also contribute to the antithrombin effect of plasma.

7. Fibrinolytic system.

Fibrin degradation products that result from fibrinolysis prevent further clotting and platelet aggregation.

Fibrinolytic system

The plasma proteins contain a euglobulin called plasminogen(profibrinolysin) that, when activated becomes a substance called plasmin(fibrinolysin), plasmin is a proteolytic enzyme that digests fibrin fibers and some other protein coagulants such as fibrinogen, factor V, factor VIII, prothrombin and factor XII.

plasminogen activators

extrinsic (exogenous):

A) Urokinase B) Streptokinase

Note: urokinase is discovered in urine and found in plasma. Streptokinase is produced by streptococcus bacteria.

Intrinsic:

a- Tissue plasminogen activator: produced by endothelial cells.

b- 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 → **Alpha2antiplasmin**

Clot Retraction and Expression of Serum

Within a few minutes after a clot is formed, it begins to contract and usually expresses most of the fluid from the clot. The fluid expressed is called serum because all its fibrinogen and most of the other clotting factors have been removed; in this way, serum differs from plasma. Serum cannot clot because it lacks these factors, but plasma can clot.

Two factors which play a vital role in clot retraction:

a. Platelets

b. Calcium (for actin and myosin contraction)

-plasma doesn't coagulate without Ca++.