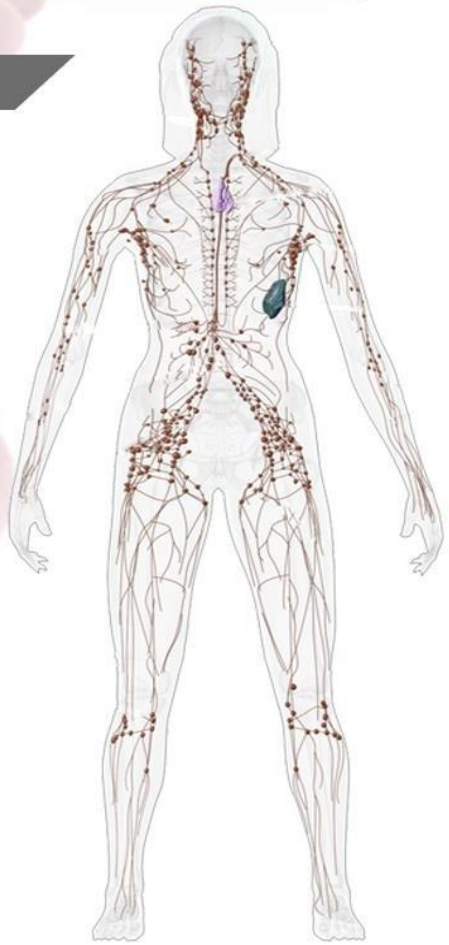
Sheet 10

Hematology and Lymphatic system

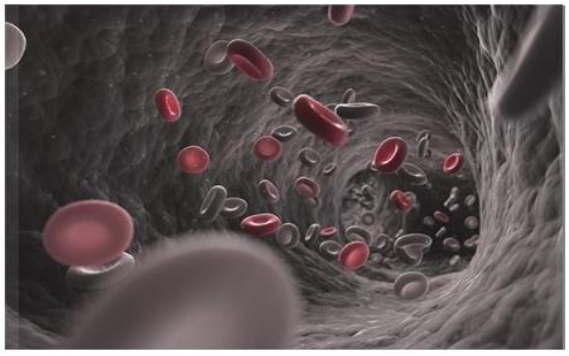
Subject | Physiology



Done by | Omar Rashdan

Corrected by |

Doctor |



Coagulation cascade

Fourth step : Formation of blood clot (coagulation) :

Clotting mechanism is activated by:

1) The release of tissue thromboplastin (factor III)
2) Activation of (factor XII)
3) Exposure of phospholipid (platelet factor 3).

Clotting factors

Factor	Name (synonyms)	Site of formation
I	Fibrinogen	Liver
II*	Prothrombin	Liver
III	Tissue thromboplastins	Tissue cells (membrane protein)
IV	Calcium ions	
V*	Labile factor	Mainly liver
VII*	Stable factor	Liver
VIII*	Anti-haemophiliac globulin A (AHG)	Platelets, RES endothelial cells, liver
vWF	von Willebrand's factor	Endothelial cells, platelets
IX*	Anti-haemophiliac globulin B (Christmas factor)	Liver
X*	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
* vitamin K-dependent * pro-cofactors

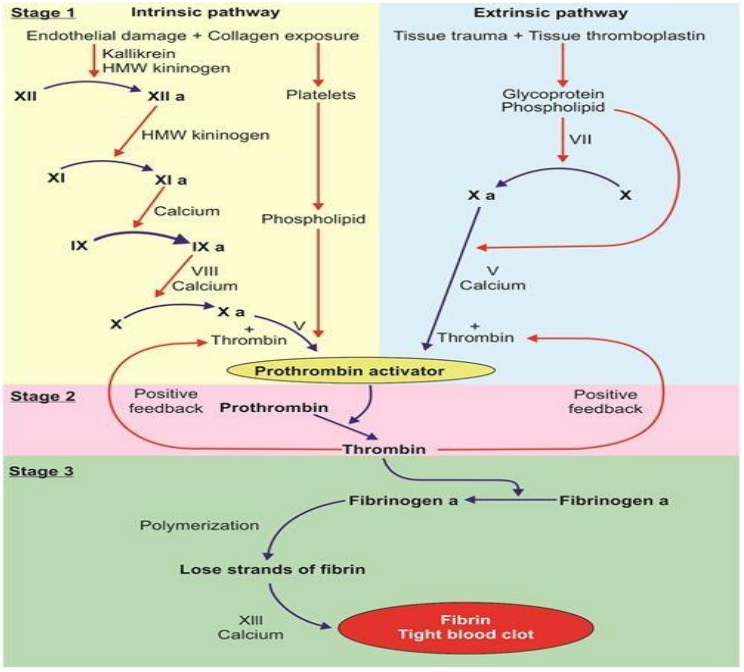
- Almost all factors are produced in the liver, so any liver disease will affect clotting.
- Factors that require vitamin K for their synthesis (vitamin–K dependent factors) are factor II, factor VII, factor IX, factor X, protein S & protein C.
- In the coagulation cascade , at each step a proenzyme is cleaved to become an active enzyme which then cleaves the next proenzyme to become an active enzyme and so on.
- Intrinsic pathway : XII→XI→IX→VIII→X
- Extrinsic pathway : III→VII→X

Clotting pathways:

1. Intrinsic pathway

2. Extrinsic pathway

3. Common pathway



Intrinsic pathway

1. Activated factor XIIa , prekallikrien and HMW-K (high molecular weightkininogen) 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 activates 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 (factor II) to form thrombin (factor II a).**

3. **Thrombin activates fibrinogen (factor I) to form fibrin.**

4. **Fibrin begins 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 a slow or delayed pathway, occurring in 6 minutes and weak, but its longlasting and more efficient and more important than the extrinsic pathway.
- Intrinsic pathway is named so because all its components are in the blood , meanwhile the extrinsic pathway , not all of 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, kallikrein, HMW-k will not cause problems (bleeding), but deficiency in factor XI will cause severe problems.**

Function of thrombin:

1) Activation of fibrinogen.
2) Activation of factors V, VIII and XIII.
3) Activation of platelets.
4) Activation of protein C

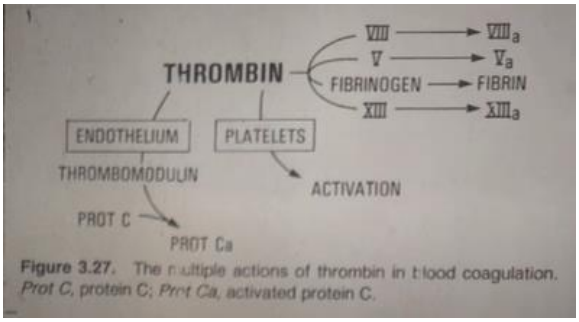


Figure 3.27. The multiple actions of thrombin in blood coagulation. *Prot C*, protein C; *Prot Ca*, activated protein C.

The Role of Calcium in Hemostasis: Without calcium, the blood doesn't coagulate. Calcium ions are required for each step in the clotting process except for the first two reactions of the intrinsic pathway.

Adequate levels of calcium are therefore necessary for normal clotting. In reality, plasma calcium levels never fall low enough to impair the clotting process, since death would have resulted from other causes (most notably tetany of respiratory muscles) long before.

Function of calcium:

1) Contraction of Actin & Myosin.
2) Secretion of granules content especially α granules.
3) Phospholipase activation.

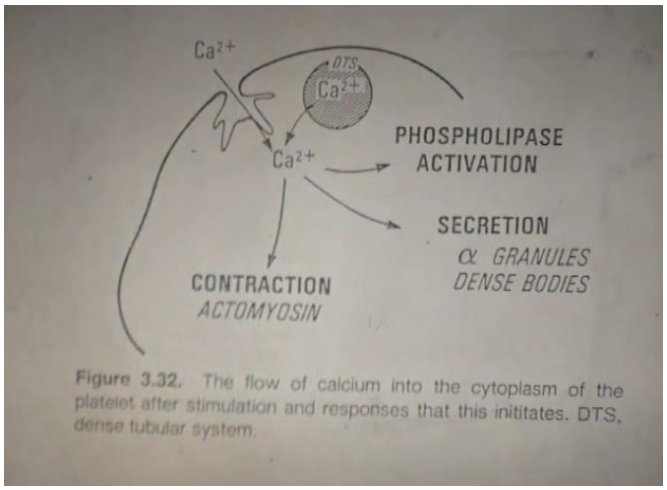


Figure 3.32. The flow of calcium into the cytoplasm of the platelet after stimulation and responses that this inititates. DTS, dense tubular system.

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 (bleeding) , therefore , normal blood fluidity should be maintained.

Factors that maintain normal fluidity of the blood:

1. Presence of heparin in the plasma (produced in basophils). → **most important factor**
2. The main clotting factors, prothrombin and fibrinogen exist in plasma in an inactive form, and part of them are removed by the portal (liver) circulation.
3. Minor clottings which occur normally and dissolve quickly. (Fibrinolytic system)

   From this process, there are two advantages:

   a- First, clotting factors are reduced to some extent as they are used for these clottings.
   b- Second, the end products of degradation of the minor clottings. (fibrin/fibrinogen degradation products) function as anticoagulants.
4. Endothelial lining of vessel is smooth and negatively charged, so it repels platelets and prevents their adhesion.
5. Antithrombin III: inhibits the action of thrombin as well as IXa, Xa, Xla and Xlla.
6. Thrombin binds to thrombomodulin, leading to activation of protein s and protein c, that in the presence of calcium inactivate factors V, VIII.

   Note : protein s & protein c require vitamin K for their synthesis.
7. **α2 macroglobulin** & **α1 antitrypsin**, also contribute to the antithrombin effect of plasma and the fibrinolytic system.

Fifth step : Clot Retraction:

Following the coagulation of blood, the clot gradually shrinks as serum is extruded from it. This is achieved by contraction of platelets.

Clot retraction time:

- The clot retraction time measures the ability of the blood clot to retract.
- In normal blood the clot retracts as follows:
  1) If a blood tube is left in the lab for two hours, there is partial retraction of the clot , the blood volume shrinks by 50%.
  2) After 24 hours , there is complete retraction of the clot.

- **Two factors which play a vital role in clot retraction:**

  A. Platelets

  B. Calcium (for actin and myosin contraction)

- When the platelet count is decreased , the clot retraction time is increased.
- The clot retraction time is mainly used in the diagnosis of hemorrhagic diseases. In purpura hemorrhagica , for example , the blood clot retraction time is greatly increased. In severe cases , there's no retraction of the clot even after 24 hours.
- Note : serum does not contain clotting factors therefore it doesn't clot , unlike plasma which does clot.

Sixth step : Clot Dissolution: (Fibrinolytic system)

The fibrin in the clot has to be lysed. This is achieved by an enzyme called plasmin.

Plasminogen → Plasmin (active form)

Plasminogen activators:

1- Endogenous Activators:

   a- Tissue plasminogen activator: produced by endothelial cells.

   b- Contact phase of coagulation.

2- Exogenous Activators:

   a- Urokinase (present in plasma and urine)

   b- Streptokinase (from streptococcus bacteria).

Plasmin function :

1) Proteolysis of fibrinogen, fibrin.

   This proteolysis produces fibrinogen degradation products which inhibit :

   A- The polymerization of fibrin

   B- Platelet aggregation.

2) Proteolysis of Factors V and VIII.

Important note : α2-antiplasmin inhibits plasmin (regulation)

Now , we said that even in healthy people minor clottings occur, but these clottings are few and dissolve immediately.

1) Sometimes, unwanted clotting is formed in the blood vessels , this is called thrombosis and the clot itself is a thrombus.
2) This clot may dissolve as we said previously.
3) Sometimes, a clot may be removed from its attachment and carried with the blood , this is called an Embolus , and the condition is called embolism.
4) An embolus may be :

i. A clot
ii. A bubble of air
iii. Fat from broken bones
iv. Pieces of debris

Thromboembolic conditions

1) Emboli can be swept by the blood through the heart & pulmonary artery to lodge in and obstruct a small artery in the lung
2) Thrombi in arteries are more dangerous than in veins especially when the artery is one that carries blood to vital regions such as the brain or heart muscle.
3) Arteriosclerosis (atherosclerosis) is the condition underlying most heart attacks

Note :

Atherosclerosis: the accumulation of lipids inside the blood vessels, so they become relatively narrow.

Arteriosclerosis: the loss of blood vessels flexibility, due to aging for example. So, vasoconstriction and vasodilatation would be much harder, thus causing rupture of the blood vessels, leading to platelets stimulation.

Causes of thrombosis in man

1) **Injury to a blood vessel by trauma**, or the application of an irritating substance leads to thrombosis , in this case the process **may begin as an activation of the extrinsic or intrinsic** pathway or as platelet adhesion , release results in intensified platelet aggregation and fibrin formation.

2) **Infections**: in the vicinity of cellulitis and abscesses the endothelium becomes injured through inflammatory responses **; these induce platelet adhesion to injured endothelium** with ADP release , platelet aggregation ,etc.

3) **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 , **with a resulting platelet deposition and clotting.**

4) **Changes in the blood , after operation and childbirth , both the number of platelets and the level of fibrinogen are increased**. An important factor leading to thrombosis is probably an **alteration in platelets stickiness** associated with alteration in the endothelium and slowing of the blood flow.

Zymogens of Serine Proteases	***Activities***
Factor XII	Binds to exposed collagen at site of vessel wall injury, activated by HMWK and kallikrein
Factor XI	Activated by factor XIIa
Factor IX	Activated by factor XIa in presence of Ca^{2+}
Factor VII	Activated by thrombin in presence of Ca^{2+}
Factor X	Activated on surface of activated platelets by tenase complex and by factor VIIa in presence of tissue factor and Ca^{2+}
Factor II	Activated on surface of activated platelets by prothrombinase complex
Cofactors	***Activities***
Factor VIII	Activated by thrombin; factor VIIIa is a cofactor in the activation of factor X by factor IXa
Factor V	Activated by thrombin; factor Va is a cofactor in the activation of prothrombin by factor Xa
Factor III (tissue factor)	A subendothelial cell-surface glycoprotein that acts as a cofactor for factor VII
Fibrinogen	***Activity***
Factor I	Cleaved by thrombin to form fibrin clot
Transglutaminase	***Activity***
Factor XIII	Activated by thrombin in presence of Ca^{2+}; stabilizes fibrin clot by covalent cross-linking
Regulatory/Other Proteins	***Activities***
von Willebrand factor	Associated with subendothelial connective tissue; serves as a bridge between platelet glycoprotein GPIb/IX and collagen
Protein C	Activated to protein Ca by thrombin bound to thrombomodulin; then degrades factors VIIIa and Va
Protein S	Acts as a cofactor of protein C; both proteins contain *gla* residues
Thrombomodulin	Protein on the surface of endothelial cells; binds thrombin, which then activates protein C
Antithrombin III	Most important coagulation inhibitor, controls activities of thrombin and factors IXa, Xa, XIa, and XIIa