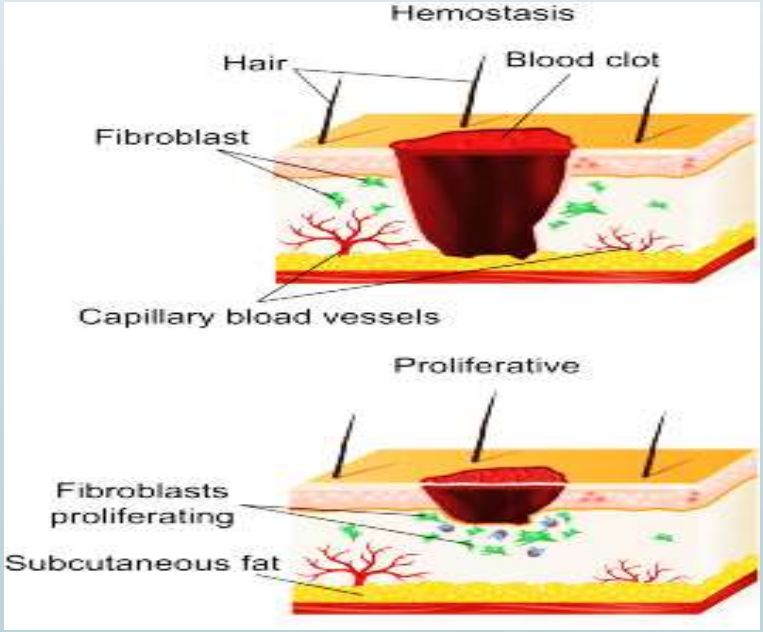
6. GENERAL OVERVIEW OF HEMOSTATIC PROCESS.



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Heamostasis

• It is the stoppage of bleeding in case of small vascular injury. It depends on the vascular wall, platelets and the clotting factors.

• **Mechanism:**

(1) Extravascular:

- Physical effects of skin and elastic tissue in closing the bl. vs.
- Biochemical effects of released substances from tissue in activation of clotting.

(**2) Vascular factors**

(3) Platelets plug

(**4) Blood coagulation**

[I] Vascular factor (local vascular spasm):

• **Causes:**

a- Direct effect of serotonin and thromboxane A2 released from platelets → V.C.

b- Injury of endothelium → ↓ EDRF → VC.

c- Pain → nervous VC reflex.

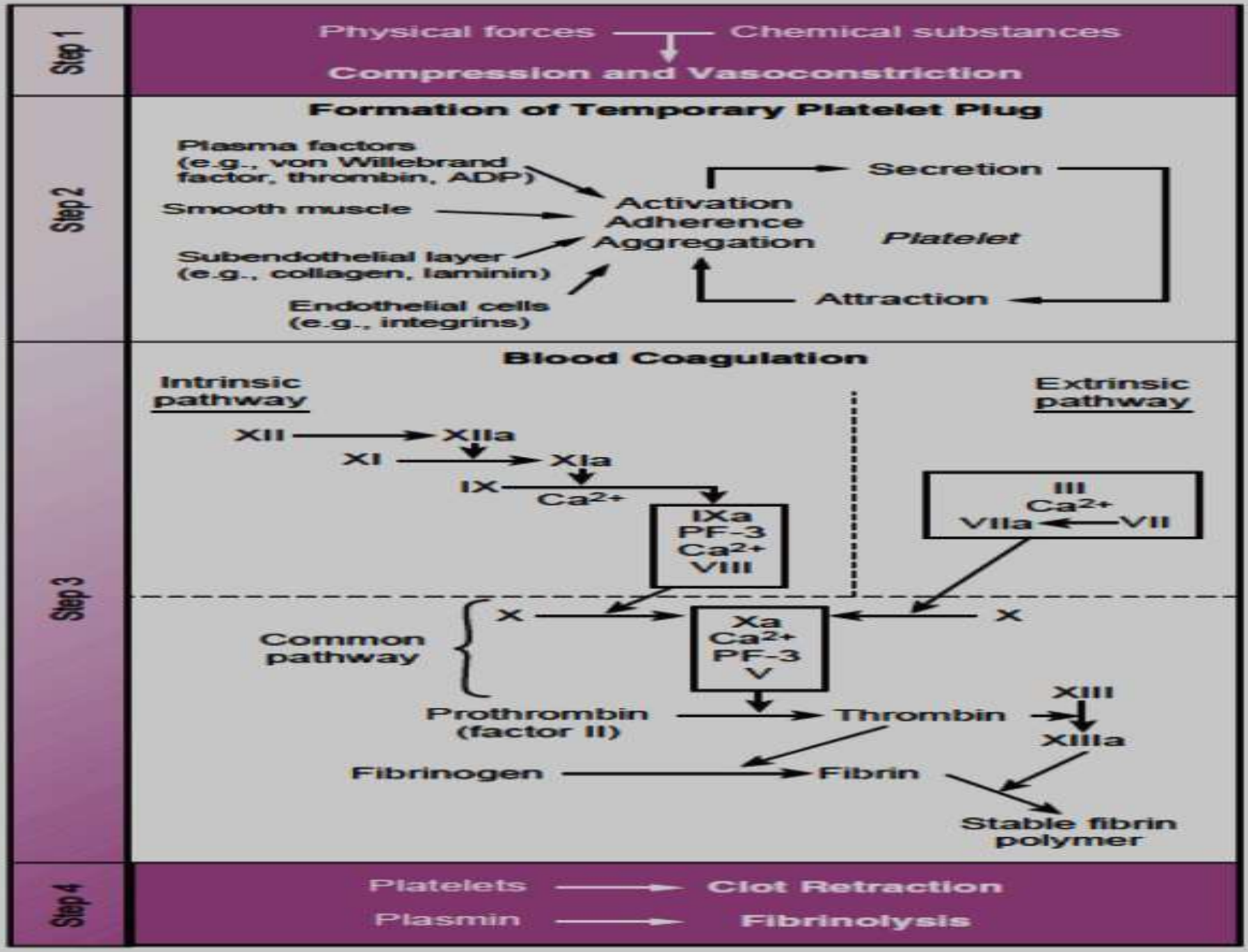
d- Local myogenic VC of injured vessel.

• **Significance:**

a- It is responsible for stop blood flow.

b- It allows time for haemostatic mechanisms to occur.

c- The reduced blood flow help contact activation of platelet and clotting factors.


Step 1
Physical forces
Chemical substances
Compression and Vasoconstriction
Step 2
Formation of Temporary Platelet Plug
Plasma factors
(e.g., von Willebrand
factor, thrombin, ADP)
Smooth muscle
Subendothelial layer
(e.g., collagen, laminin)
Endothelial cells
(e.g., integrins)
Activation
Adherence
Aggregation
Secretion
Platelet
Attraction
Step 3
Blood Coagulation
Intrinsic
pathway
Extrinsic
pathway
XII
XIIa
XI
XIa
IX
Ca2+
IXa
PF-3
Ca2+
VIII
III
Ca2+
VIIa
VII
Common
pathway
X
Xa
Ca2+
PF-3
V
X
Prothrombin
(factor II)
Thrombin
XIII
XIIIa
Fibrinogen
Fibrin
Stable fibrin
polymer
Step 4
Platelets
Clot Retraction
Plasmin
Fibrinolysis

[II] Formation of platelet plug: (Platelet function):

The main function of platelets is the formation of mechanical plug to close the vascular injury in the following steps:

1)Platelet adhesion:

- Following blood vessel injury, platelets adhere to the exposed sub-endothelial collagen and myofibrils.

- Adhesion **depends on**:

a. A surface membrane glycoportein.

b. Von-Willebrand factor.

2) Platelets release occurs as the following:

a-The platelets swell and becomes irregular with numerous processes which facilitate the interaction between adjacent platelets.

b- The contractile proteins of platelets contract causing the release of the contents of platelets such as ADP, serotonin, VWF, fibrinogen and platelet factor .

c- Platelets enzymes form thromboxane A2 which released in the blood. Thromboxane A2 → ↑ platelet cAMP → release of platelets contents required for aggregation and severe V.C.

3)Platelet aggregation:

- Released ADP and thromboxaneA2 cause the platelet to swell and adhere to each other (aggregation) leading to further release and more aggregation and so on.

- The result is the formation **of platelet plug** which closes the injured area.

4)Platelet plug:

- At first, the plug is loose then becomes firm and tight by contraction of platelets contractile proteins and by fibrin threads which attached to the injured vessel wall forming tight plug.

- The normal endothelial cells around the injury release prostacyclin which causes limitation of the plug to site of the injury by inhibition of platelet aggregation and causes vasodilatation to limit the vaso-constrictive effect of thromboxaneA2.

- Importance of the plug:

a. It stops blood loss from small vessels.

b. It closes the minute ruptures of very small vessels, which occur hundreds of times daily.

c. The chemicals released from the plug help other mechanisms of haemostasis as the following:

- Serotonin and thromboxane A2 cause vasoconstriction.

- Platelet pro-coagulant activity: after platelet aggregation, the membrane phospholipid (platelet factor 3) factor V and fibrinogen are exposed and initiate intrinsic clotting.

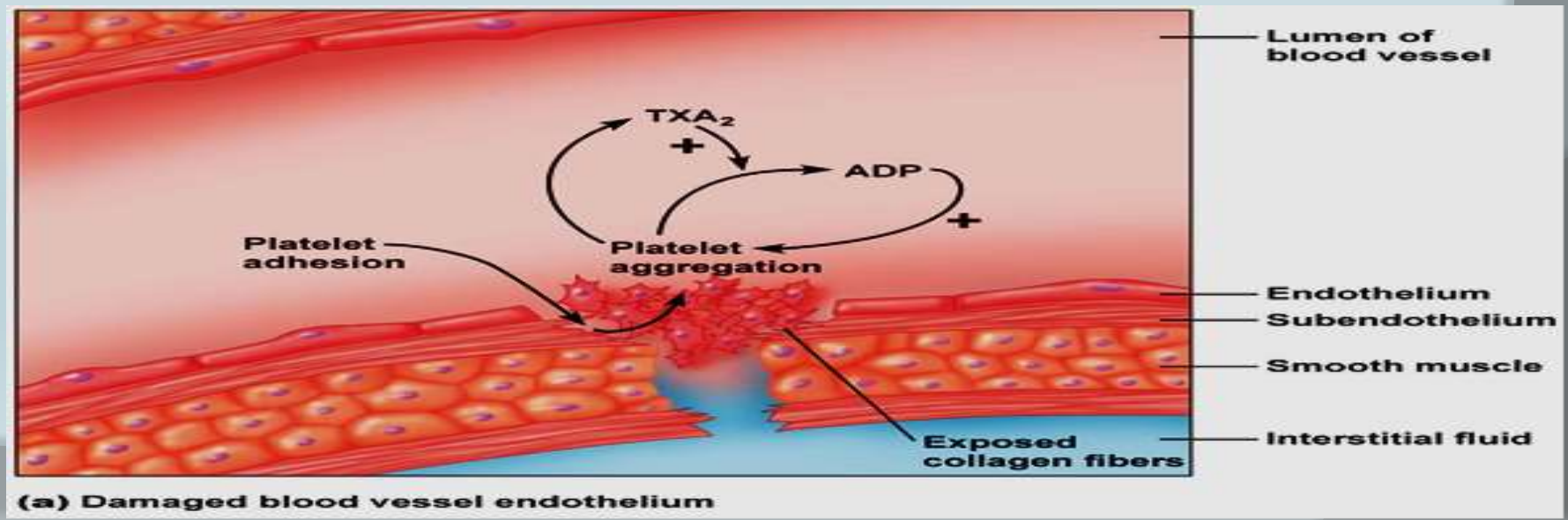
- Factor XIII helps in stabilization of the blood clot.

- Platelet factor 4 [heparin antagonist] neutralizes heparin and prevents its inhibitory effect on blood clot.

5) Platelet fusion: by ADP and enzymes.

6) Platelet release thrombasthenin & ATP → clot retraction.

7) Platelet derived growth factor stimulate growth of the vascular endothelial cells, smooth muscles and fibroblasts which help the repair of the damaged vessels.



(a) Damaged blood vessel endothelium

[III] Blood coagulation

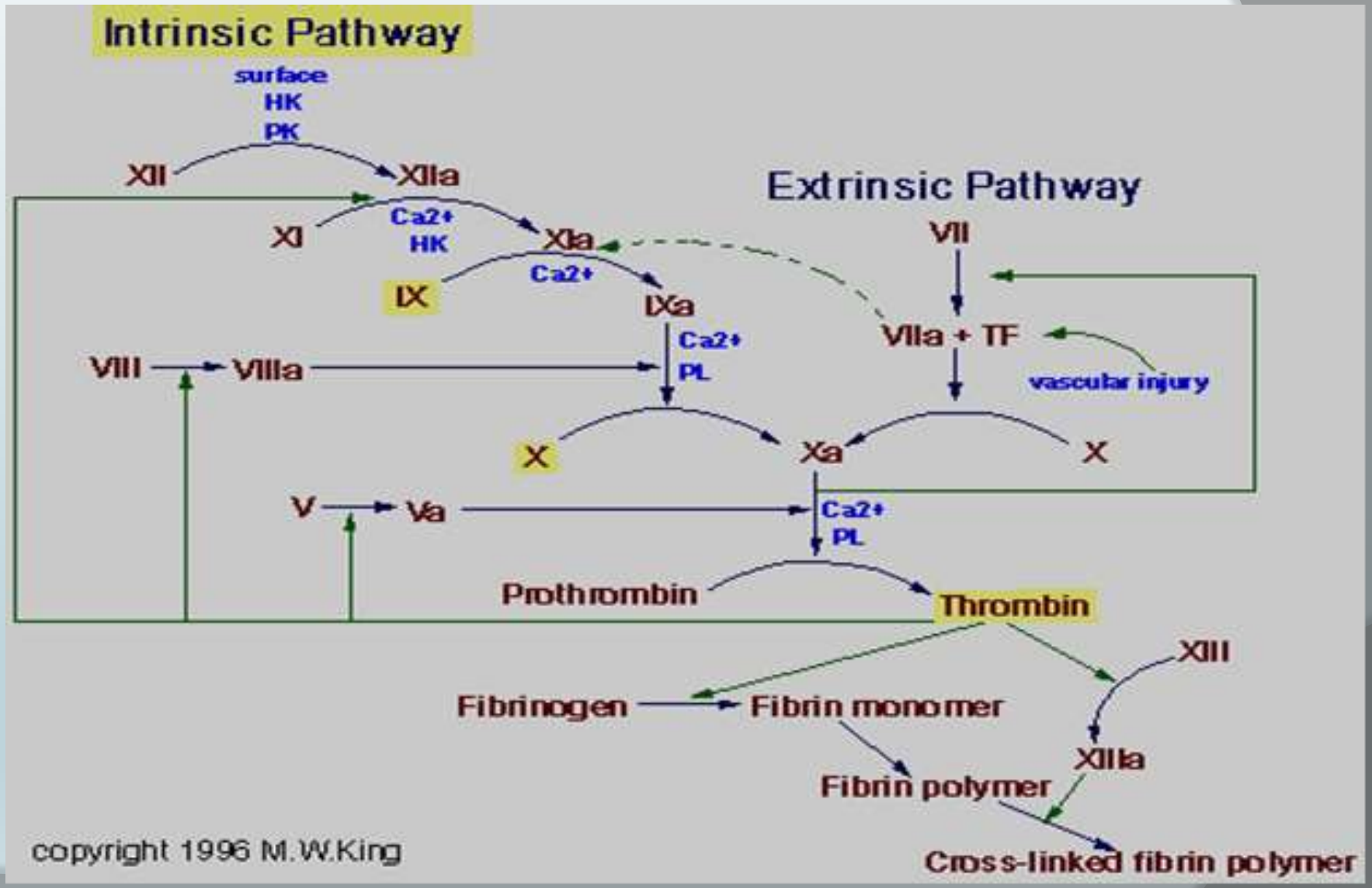
• It is the formation of blood clot as a network of insoluble fibrin entangling blood cells.
• It needs the following clotting factors:

- I (Fibrinogen) - II (prothrombin)
- III (thromboplastic) - IV (Calcium)
- V (Labile factor) - VII (stable factor)
- VIII (antihaemophilia globulin) - IX (christmas factor)
- X (Stuart prower factor)
- XI (plasma thromboplastin antecadent).
- XII (Hageman factor) -XIII(fibrin stabilizing factor)
- Platelet factor-3 (phospholipid) - VWF
- High molecular weight kininogen and prekallikrein.

• **The clotting factors are formed in:**

- **The liver**: as ϒ-globulins in an inactive form. Some clotting factors require vit. K in their synthesis from the liver (factor II,VII,XI and X).
-**Megakaryocytes:** Share in formation of fibrinogen, Factor V, XIII and VWF. These factors are carried and stored in the alpha granules in the platelets.
- **Macrophages**: Share in synthesis of factors V, VII, IX and X.
- **Endothelial cells** form VWF.

Mechanism of blood coagulation: (Coagulation cascade)



*Steps of blood clotting :

[1] Formation of Prothrombin activator:

A- Extrinsic pathway:

1-Injury of the blood vessels and surrounding tissue causes release of tissue thromboplastin (lipoprotein mixture) which activate factor VII which stimulate factor X in the presence of Ca++.[It is called extrinsic because it depends on external factors from the tissue]

2-Activated factor X with factor Va and tissue phospholipids and calcium form enzyme complex called prothrombin activators.

3-The extrinsic mechanism takes few seconds and depends on the degree of tissue injury and quantities of factor VII, V and X.

B- Intrinsic pathway:

1- When the blood comes in contact with subendothelial collagen in injured bl.vs. or with wettable surface as test tube, factor XII is activated to active XII (XIIa) which aided by kallikrein.

2- Also, subendothelial collagen or the wettable surface activate the platelet to release platelets phospholipids .

3- Then factor XIIa activates factor XI in presence of high molecular weight kininogen (HMWK).

4- Then factor XIa activates factor IX .

5- Then factor IXa + Factor VIII + platelet phospholipids in presence of calcium ions activate factor X.

6- Activated factor X with factor V and platelet phospholipids to form enzyme complex called prothrombin activator.

-Interaction between the extrinsic and intrinsic mechanisms:

1- After injury the both mechanisms are activated at the same time by tissue factor and platelet factor.

2- The intrinsic mechanism stops the blood in the injured vessel, whereas the extrinsic mechanism clots the blood escapes into the tissue.

3- Both pathways begin at the same time but extrinsic take 15-20 seconds and intrinsic 2-10 minutes.

4- Both pathways are complementary as factor VIIa activate IX also XIIa, X1, Xa and thrombin activate VII.

[2] Conversion of Prothrombin to thrombin:

By the prothrombin activators the prothrombin changed into thrombin in the presence of calcium and then thrombin acts on prothrombin itself producing more thrombin (positive feed back effect) Then thrombin acts as proteolytic enzyme and have the following actions:

1-Conversion of fibrinogen to fibrin threads.

2-Thrombin activates some of the clotting factors (V,VII,VIII) which are required for its formation in a positive feed back, Thrombin increases platelet adhesion and aggregation.

[3] Conversion of fibrinogen to fibrin (formation of fibrin clot):

• Thrombin splits small negatively charged peptide fragments from the fibrinogen molecules (removing the repulsive forces from the molecules) and allowing the remainder to polymerize to form fibrin polymers or threads. These threads adhere to the injured blood vessel wall forming loose net like meshwork that traps the blood cells forming red soft blood clot.

• **Stabilization of blood clot** by activated factor XIII which activated by thrombin. Factor XIIIa strengthens the fibrin clot by forming strong bonds between fibrin polymers.

• **Clot retraction**: the fibrin clot contains large number of platelets which release factor XIII and attached to the fibrin threads ,also their contractile protein (actin, myosin and thrombosthenin) contract leading to the fibrin meshwork shrinks and becomes stronger and clear yellowish serum is squeezed from the clot. This step is stimulated by thrombin and calcium ions released from the platelets. This step makes the clot more dense and strong and also pulls the edges of the wound together facilitating the repair of the injury.

Thank You