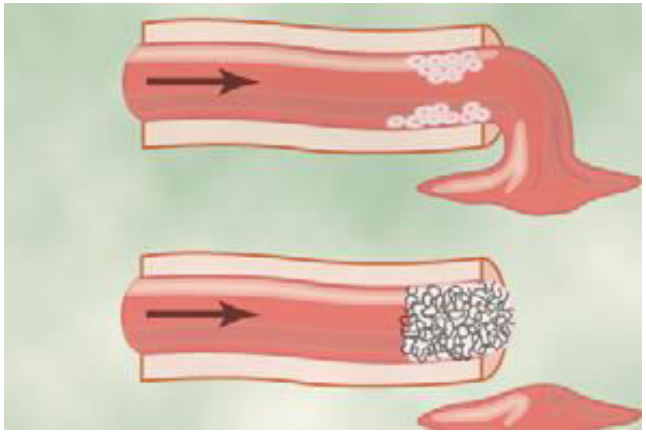
UG SEM-IV
CC-9T: Animal Physiology:Life Sustaining Systems
Unit 3: Physiology of Circulation

Haemostasis

Blood clotting system, Fibrinolytic system



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Definition:

- Spontaneous arrest /prevention of bleeding from injured/ damaged vessels by the physiological process.

Events in Hemostasis

- (1) vascular constriction
- (2) formation of a platelet plug
- (3) formation of a blood clot as a result of blood coagulation
- (4) eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

1. Vasoconstriction:

- Trauma to the vessel wall itself causes the smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel.

- The contraction results from

  (1) local myogenic spasm,

  (2) local autacoid factors from the traumatized tissues and blood platelets, and

  (3) nervous reflexes.

- **Initial vasoconstriction (transient)**

1. Immediate
2. Few cm in both the direction from the point of injury,
3. Degree of spasm proportional to the degree of traume,
4. Effective to stop bleeding for small vessels

- **Humoral** facilitation of vasoconstriction

(several minutes to even hours)

1. Platelets come in contact with damaged endothelium & collagen
2. Release 5HT , other vasoconstrictor: *thromboxane A2*

(2) Formation of a platelet plug

(temporary haemostatic plug)

- 1. Platelet Adhesion

  i) Swelling ii)irregular shape with pseudopodia

  iii) forceful contraction of contractile proteins

  iv) releaseing granules v)sticky, adhere to collagen

- 2.Platelet Activation

  release ADP & *thromboxane A2,*

  activation of nearby platelets

- 3.Platelet Aggregation

  PAF- cytokine secreted by neutrophil, monocytes, platelet cell membrane lipid

- 4.Formation of Plug

  initially loose plug, decreaseing blood loss

(3) formation of a blood clot as a result of blood coagulation (definitive haemostatic plug)

- The clot begins to develop within 15 to 20 Seconds for severe trauma and within 1 to 2 minutes for minor trauma.

- Activator substances from the traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process.

- Within 3 to 6 minutes after rupture of a vessel, if the vessel opening is not too large, the entire opening or broken end of the vessel is filled with clot.
- After 20 minutes to an hour, the clot retracts; this closes the vessel still further

Mechanism of blood coagulation

- Procoagulants - that promote coagulation
- Anticoagulants - that inhibit coagulation

- Whether blood will coagulate or not depends on the balance between these two groups of substances.

Mechanism of blood coagulation

- 1. Formation of **Prothrombin activator**
- 2.Conversion of **Prothrombin to Thrombin**
- 3. Conversion of **Fibrinogen to Fibrin**

Formation of **Prothrombin activator**

- (1) the **extrinsic pathway** that begins with trauma to the vascular wall and extravascular tissues

- (2) the **intrinsic pathway** that begins in the blood itself.(blood trauma, exposure of blood to collagen underlying damaged endothelium)

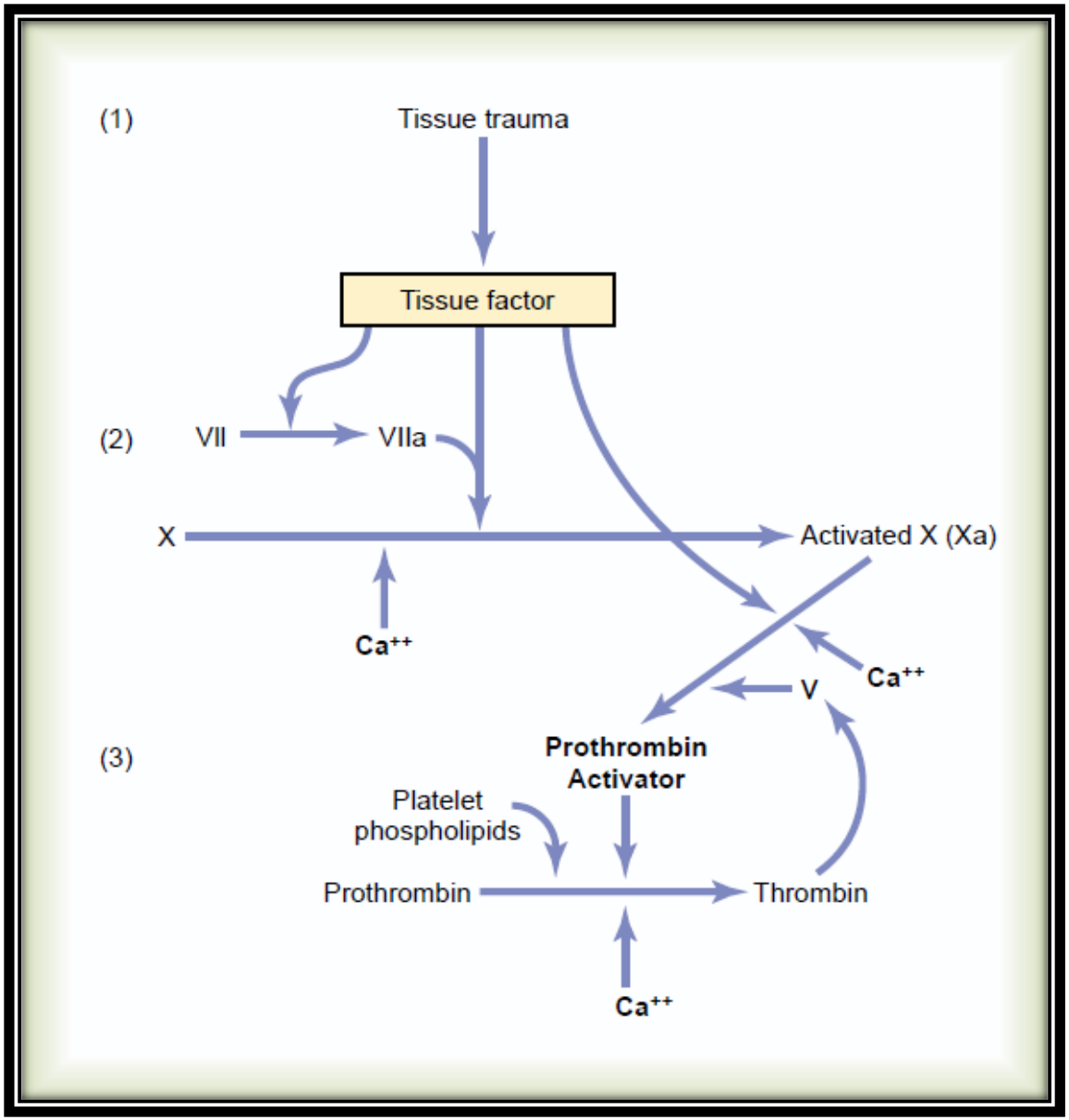
- **Two pathways** interact constantly with each other
- Mediated by a series of different plasma proteins called blood clotting factors
- Most of these are inactive forms of proteolytic enzymes
- When converted to the active forms, their enzymatic actions cause the successive, cascading reactions of the clotting process.

Clotting Factors in Blood and Their Synonyms

Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight) kininogen
Platelets	

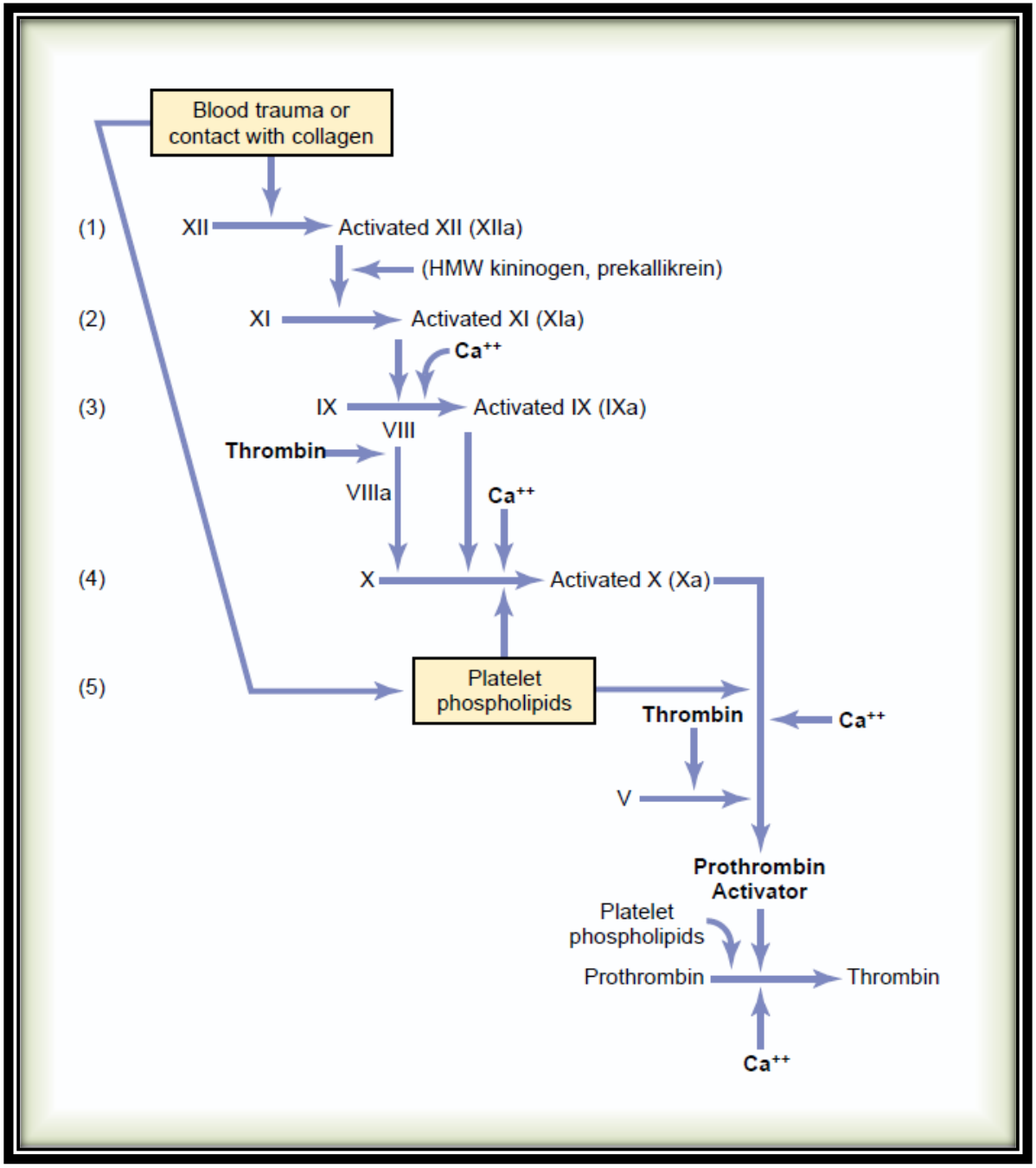
Extrinsic pathway

- Release of tissue factor (thromboplastin-phospholipid & lipoprotein)
- Activation of Factor X—role of Factor VII and tissue factor.
- Effect of activated Factor X (Xa) to form prothrombin activator—(Xa + tissue phospholipids + V + Ca++).


(1)
Tissue trauma
Tissue factor
(2)
VII
VIIa
X
Activated X (Xa)
Ca++
Ca++
V
(3)
Prothrombin Activator
Platelet phospholipids
Prothrombin
Thrombin
Ca++

Intrinsic pathway

- Activation of Factor XII & release of platelet phospholipids
- Activation of Factor XI
- Activation of Factor IX by activated Factor XI.
- Activation of Factor X—role of Factor VIII
- Action of activated Factor X to form prothrombin activator—role of Factor V


Blood trauma or contact with collagen
(1)
XII
Activated XII (XIIa)
(HMW kininogen, prekallikrein)
(2)
XI
Activated XI (XIa)
Ca++
(3)
IX
Activated IX (IXa)
VIII
Thrombin
VIIIa
Ca++
(4)
X
Activated X (Xa)
(5)
Platelet phospholipids
Thrombin
Ca++
V
Prothrombin Activator
Platelet phospholipids
Prothrombin
Thrombin
Ca++

2.Conversion of **Prothrombin to Thrombin**

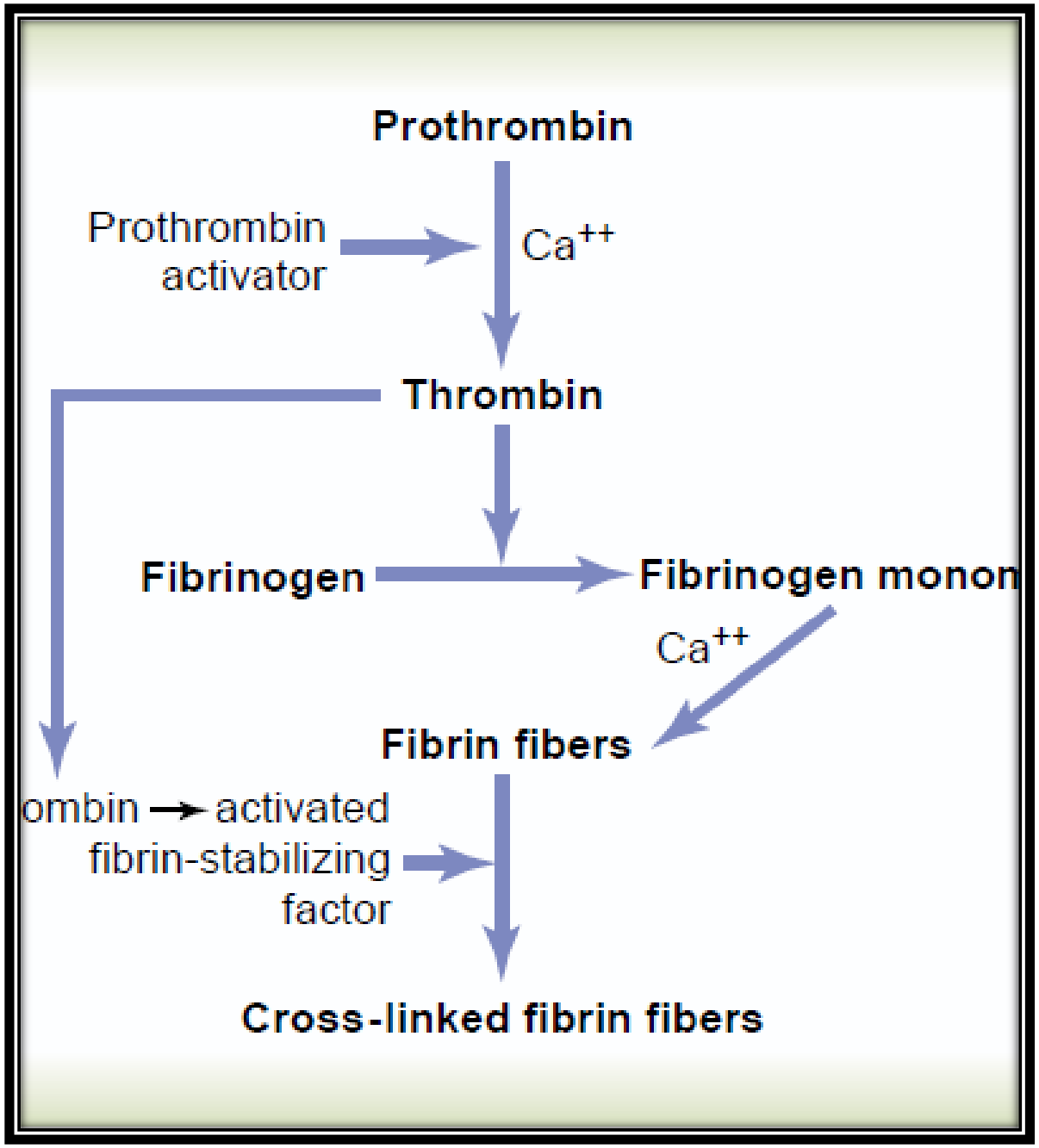
- an α 2-globulin plasma protein
- MW- 68,700 Da.
- concentration - 40 mg/dl in normal plasma .
- It is an unstable protein that can split easily into smaller compounds
- thrombin, MW- *33,700,*
- Hepatic synthesis- require vit K

- Prothrombin activator catalyzes conversion of prothrombin into thrombin in presence of ca++.

- This occurs on the surface of platelets which form the platelet plug at the site of injury.

Roles played by Thrombin

- Conversion of fibrinogen to fibrin
- Accelerates the rate of prothrombin activator formation by Positive feedback mechanism
- Activates protein C (ANTICOAGULANT)


Prothrombin
Prothrombin activator
Ca++
Thrombin
Fibrinogen
Fibrinogen monon
Ca++
Fibrin fibers
ombin → activated fibrin-stabilizing factor
Cross-linked fibrin fibers

3. Conversion of **Fibrinogen to Fibrin**

- Fibrinogen – soluble plasma protein.
- MW = 340,000
- concentration 100 to 700 mg/dl.
- 6 polypeptide chains each with 450 aa
- Fibrinogen is formed in the liver

- During proteolysis 4 polypeptide chains are removed

Steps:

- Proteolysis

Soluble fibrinogen —(thrombin)→ fibrin monomer + peptide

- Polymerization

fibrin monomer ⟶ fibrin polymer(soluble fibrin clot)

- Stabilization of fibrin polymer

Fibrin polymer —(III & XIII(FSF),Ca++)→ insoluble fibrin clot

Formation of the Clot

- **Blood Clot.**

  The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, and plasma. The fibrin fibers also adhere to damaged surfaces of blood vessels; therefore, the blood clot becomes adherent to any vascular opening and thereby prevents further blood loss.

(4)Fibrous Organization or Dissolution of the Blood Clot

- Once a blood clot has formed, it can follow one of two courses:

- (1) It can become invaded by ***fibroblasts,*** which subsequently form connective tissue all through the clot
- (2) it can dissolve.

- The usual course for a clot that forms in a small hole of a vessel wall is invasion by fibroblasts, beginning within a few hours after the clot is formed (which is promoted at least partially by growth factor secreted by platelets). This continues to complete organization of the clot into fibrous tissue within about 1 to 2 weeks.

- Conversely, when excess blood has leaked into the tissues and tissue clots have occurred where they are not needed, special substances within the clot itself usually become activated. These function as enzymes to dissolve the clot.

Clot Retraction—Serum

- The process of contraction of blood clot and oozing of serum is called clot retraction

- Within a few minutes after a clot is formed, it begins to contract and usually squeezes out most of the fluid (serum) from the clot within 20 to 60 minutes.

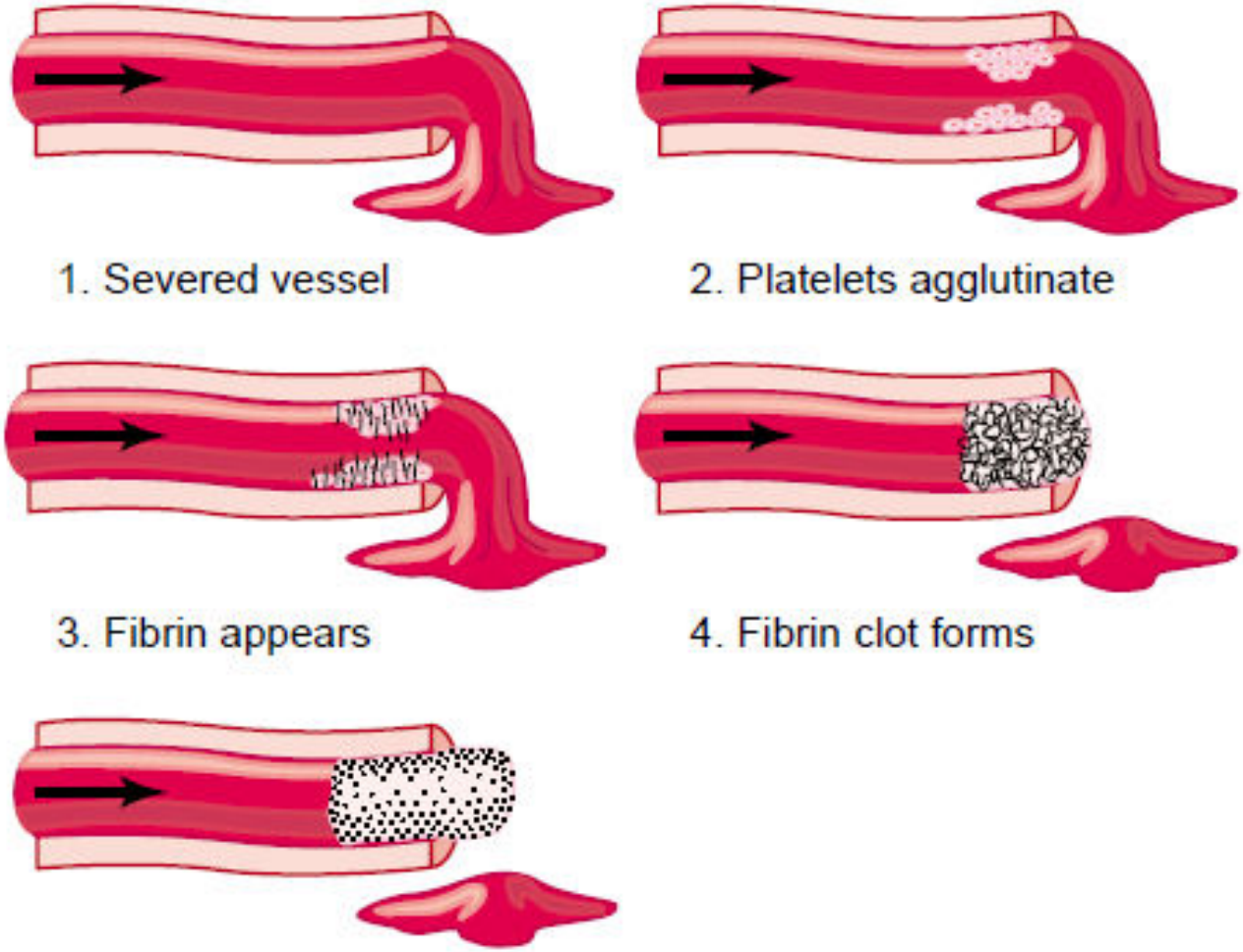
- Platelets are necessary for clot retraction. Platelets become attached to the fibrin fibres of the clot in such a way that they actually bond different fibres together.

- The contractile proteins (thrombosthenin, actin, and myosin) present in the cytoplasm of platelets cause strong contraction of the platelet spicules attached to the fibrin fibers.

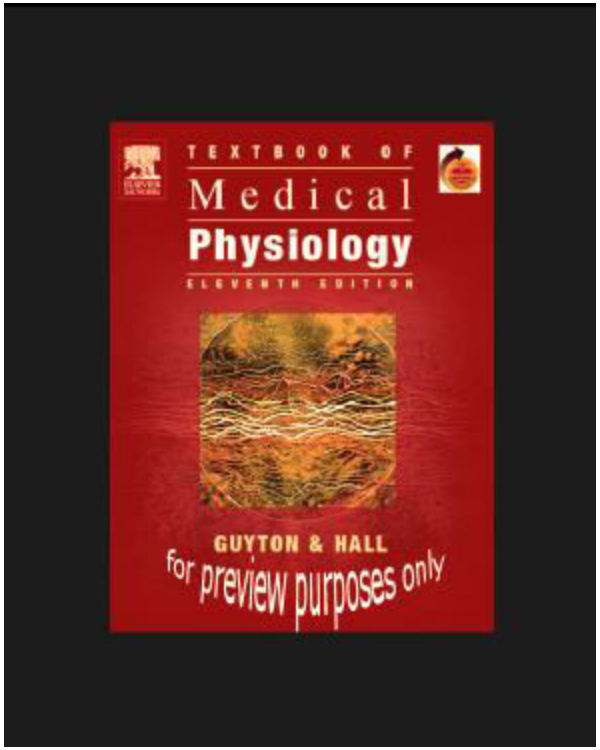
- This helps to compress the fibrin meshwork into a smaller mass.

- The contraction is activated and accelerated by thrombin as well as by calcium ions released from calcium stores in the mitochondria, endoplasmic reticulum, and Golgi apparatus of the platelets.

- As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to the ultimate state of hemostasis.


1. Severed vessel
2. Platelets agglutinate
3. Fibrin appears
4. Fibrin clot forms
5. Clot retraction occurs

Reference: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