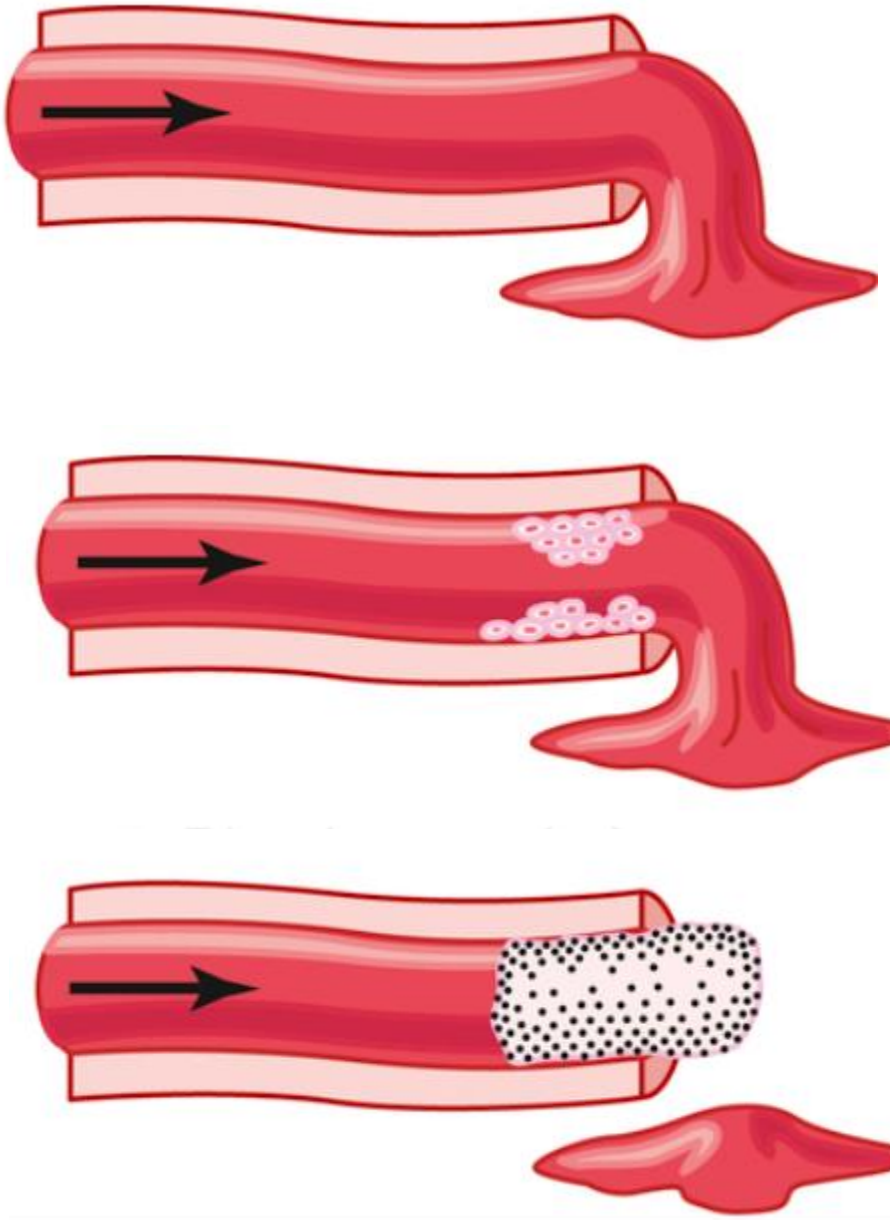
Hemostasis

Events of hemostasis

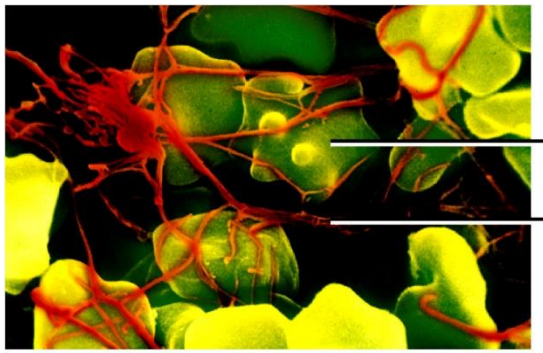
Hemostasis means prevention of blood loss and includes the following events:

(1) Vascular constriction.
(2) Formation of a platelet plug.
(3) Formation of a blood clot as a result of blood coagulation.
(4) Fibrous organization or dissolution of the blood clot

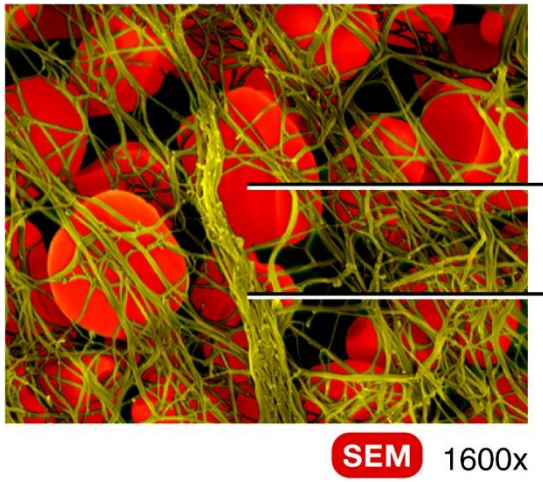


Hemostasis 3. Blood clot

- Series of chemical reactions culminating in formation of fibrin threads.
- Clotting (coagulation) factors – Ca^{2+}, several inactive enzymes, various molecules associated with platelets or released by damaged tissues.



(a) Early stage

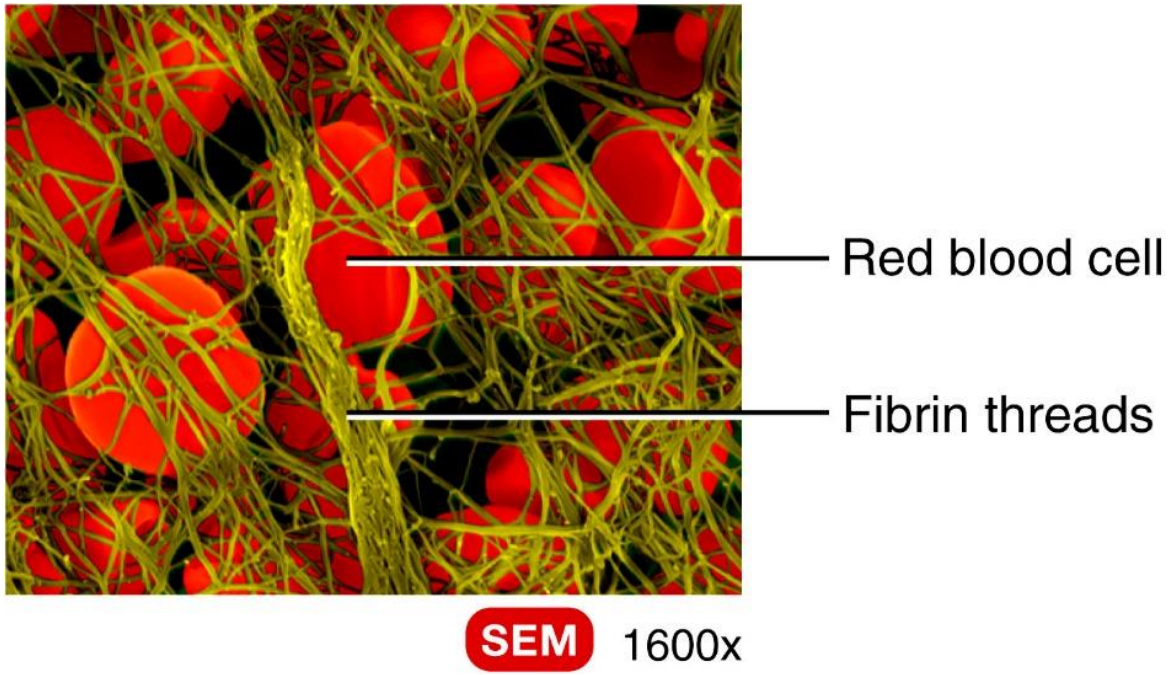


(d) Red blood cells trapped in fibrin threads

Hemostasis 3. Blood clot

- 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, thereby prevents further blood loss.



(d) Red blood cells trapped in fibrin threads

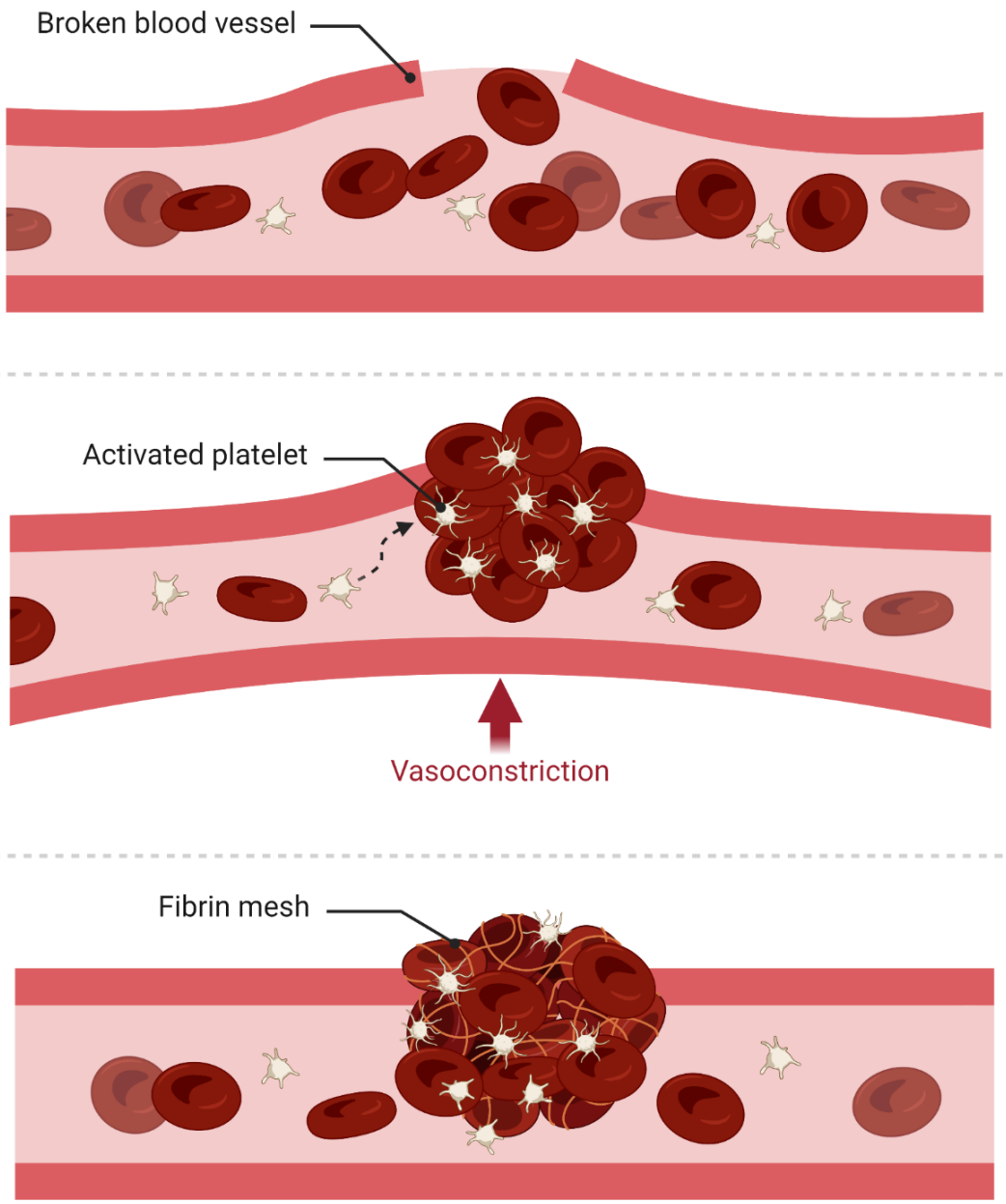
Figure 19.10d Tortora - PAP 12/e

Hemostasis 3. Clot retraction

- Within a few minutes after a clot is formed, platelets begin to contract and usually express most of the fluid from the clot within 20 to 60 minutes.

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

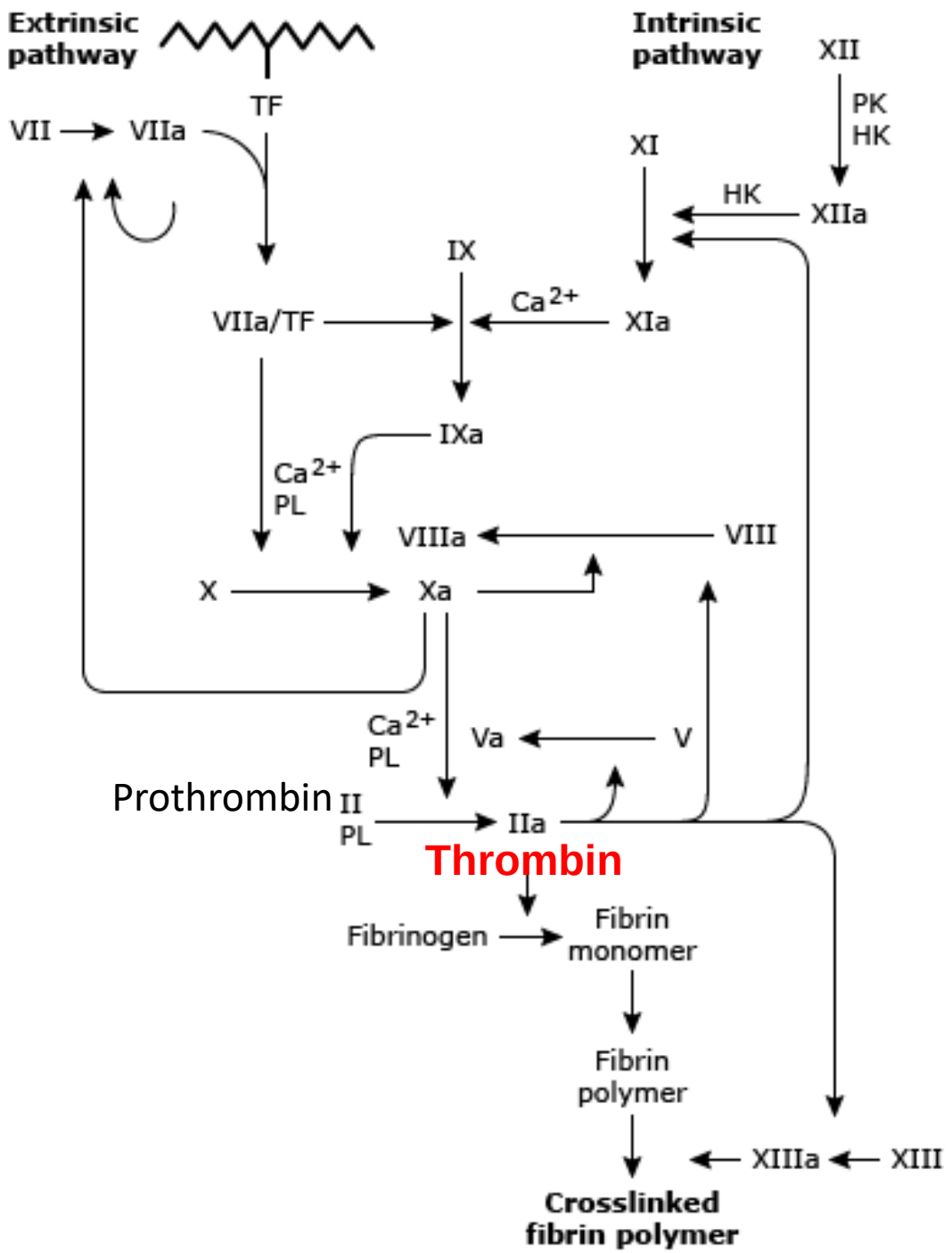
- **Serum:** is blood plasma minus its fibrinogen and most of the other clotting factors.

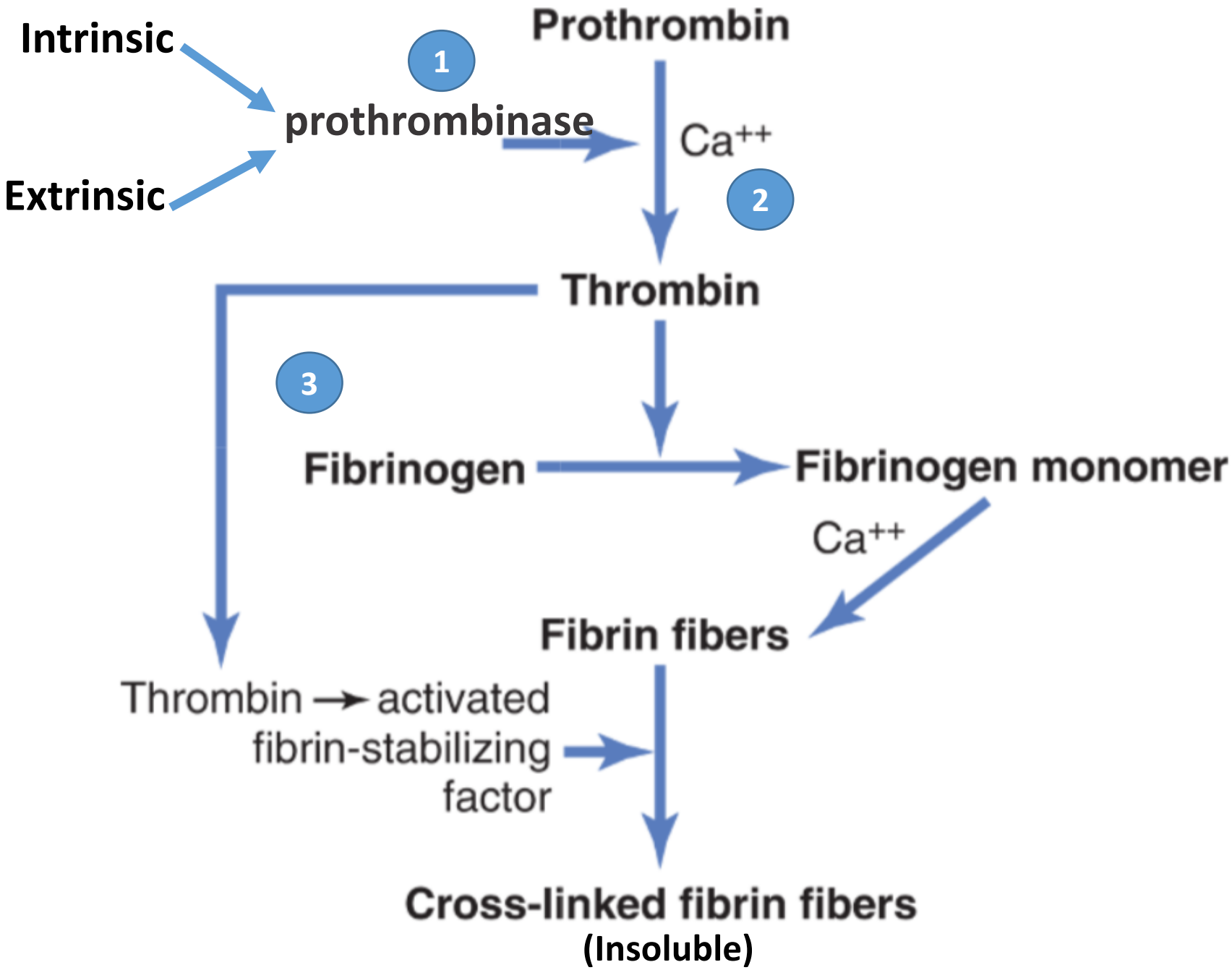


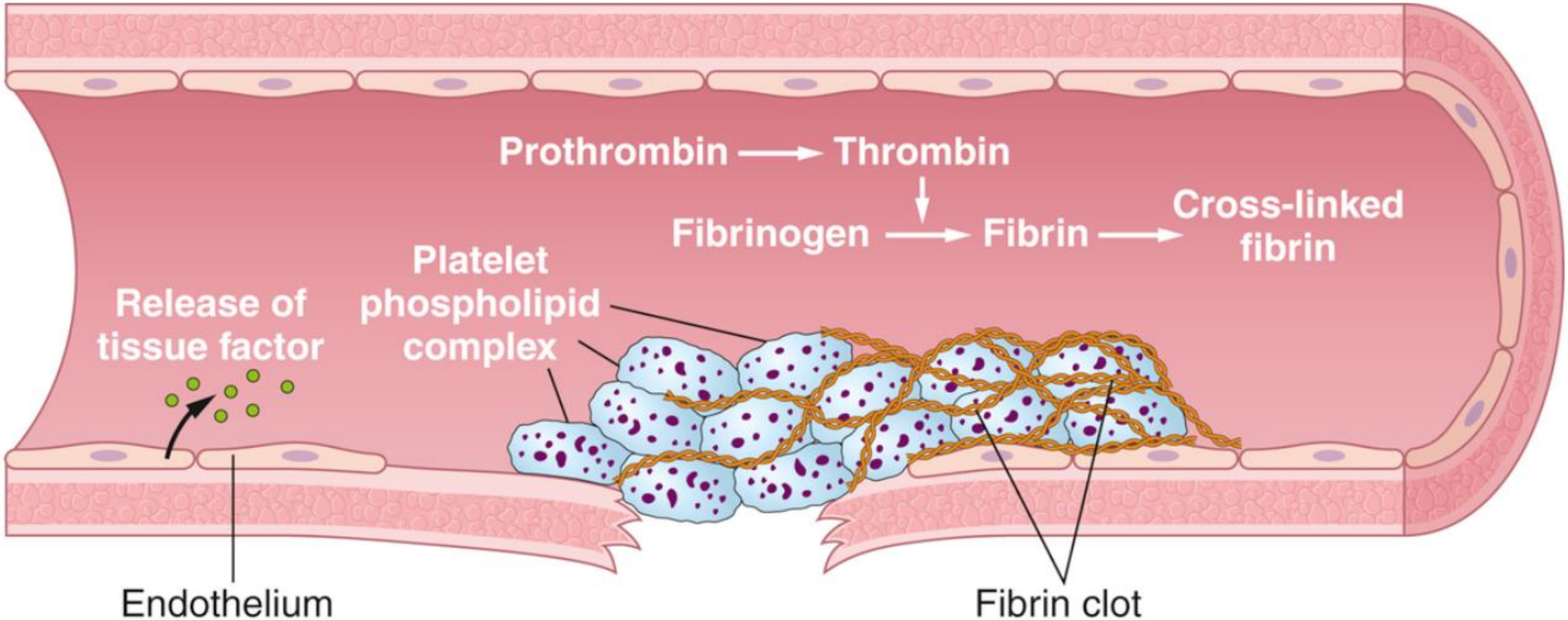
Hemostasis

3. Blood coagulation

1. Extrinsic or intrinsic pathways lead to formation of prothrombinase.
2. Prothrombinase converts prothrombin into thrombin
3. Thrombin converts fibrinogen (soluble) into fibrin (insoluble) forming the threads of the clot




Intrinsic
Extrinsic
1
prothrombinase
Prothrombin
Ca++
2
Thrombin
3
Fibrinogen
Fibrinogen monomer
Ca++
Fibrin fibers
Thrombin → activated fibrin-stabilizing factor
Cross-linked fibrin fibers
(Insoluble)


Prothrombin
Thrombin
Fibrinogen
Fibrin
Cross-linked fibrin
Platelet phospholipid complex
Release of tissue factor
Endothelium
Fibrin clot

Hemostasis 3. Prothrombin and Thrombin

- Prothrombin is a plasma protein (α2-globulin).
- It is an unstable protein that can split easily into smaller compounds, one of which is thrombin (half MW).
- Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting.
- Vitamin K is required by the liver for normal activation of prothrombin, as well as a few other clotting factors.
- Much of the prothrombin first attaches to prothrombin receptors on the platelets already bound to the damaged tissue.

3. Action of Thrombin on Fibrinogen to Form Fibrin

- Thrombin is an enzyme with weak proteolytic capabilities.
- It acts on fibrinogen to remove four low-molecular-weight peptides from each molecule of fibrinogen, forming one molecule of fibrin monomer.
- Fibrin monomer has the automatic capability to polymerize with other fibrin monomer molecules to form fibrin fibers.

Hemostasis 3. Action of Thrombin on Fibrinogen to Form Fibrin

- In the early stages of polymerization, the fibrin monomer molecules are held together by **weak noncovalent** hydrogen bonding (weak clot).
- **Fibrin-stabilizing factor** that is present in small amounts in normal plasma **globulins** but is also released from **platelets** entrapped in the clot (**inactive**).
- **Thrombin** activates the fibrin-stabilizing factor which cause **covalent bonds** between more and more of the fibrin monomer molecules, as well as **multiple cross-linkages** between adjacent fibrin fibers, thus adding **strength** of the fibrin meshwork.

Hemostasis Fibrinogen

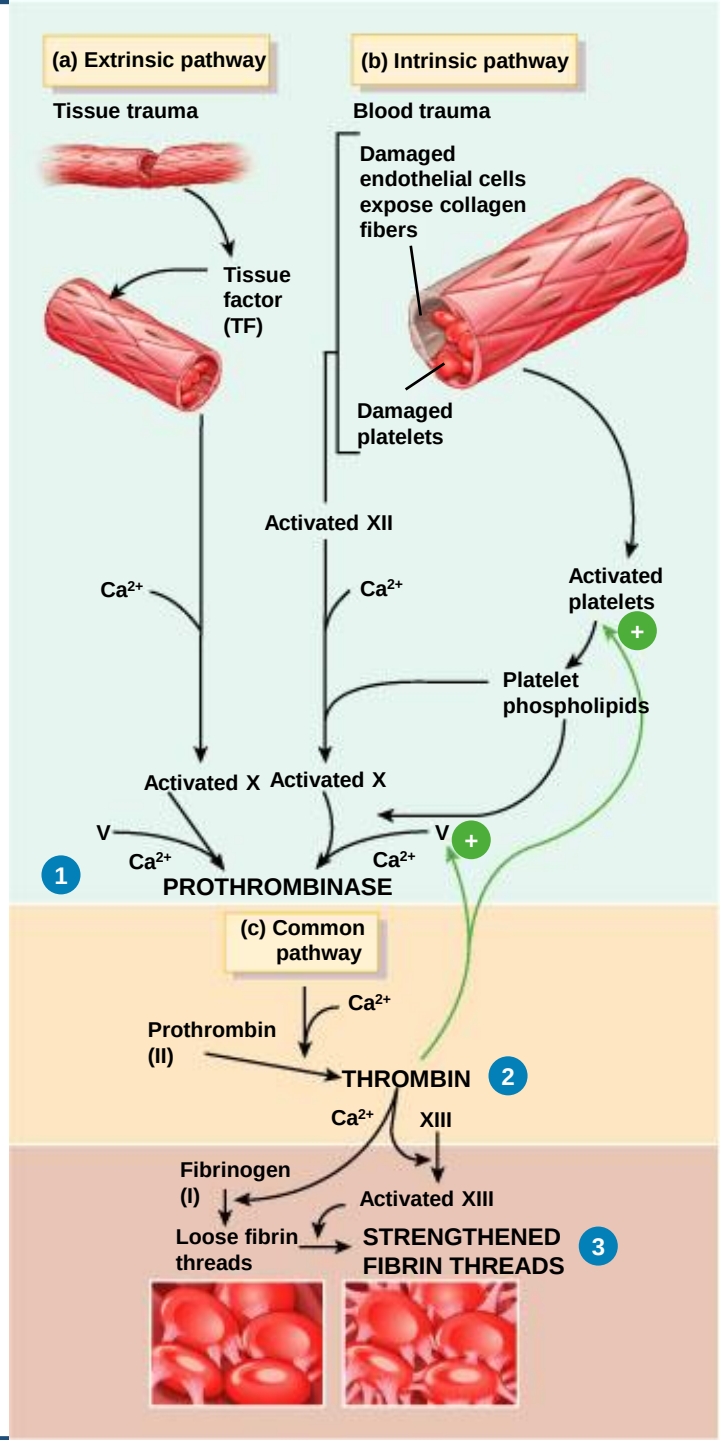
- Fibrinogen is a high-molecular-weight protein that occurs in the plasma.
- Fibrinogen is formed in the liver.
- Because of its large molecular size, little fibrinogen normally leaks from the blood vessels into the interstitial fluids, and because fibrinogen is one of the essential factors in the coagulation process, interstitial fluids ordinarily do not coagulate.

Hemostasis 3. Blood coagulation

- Prothrombin activator is generally considered to be formed in two ways:

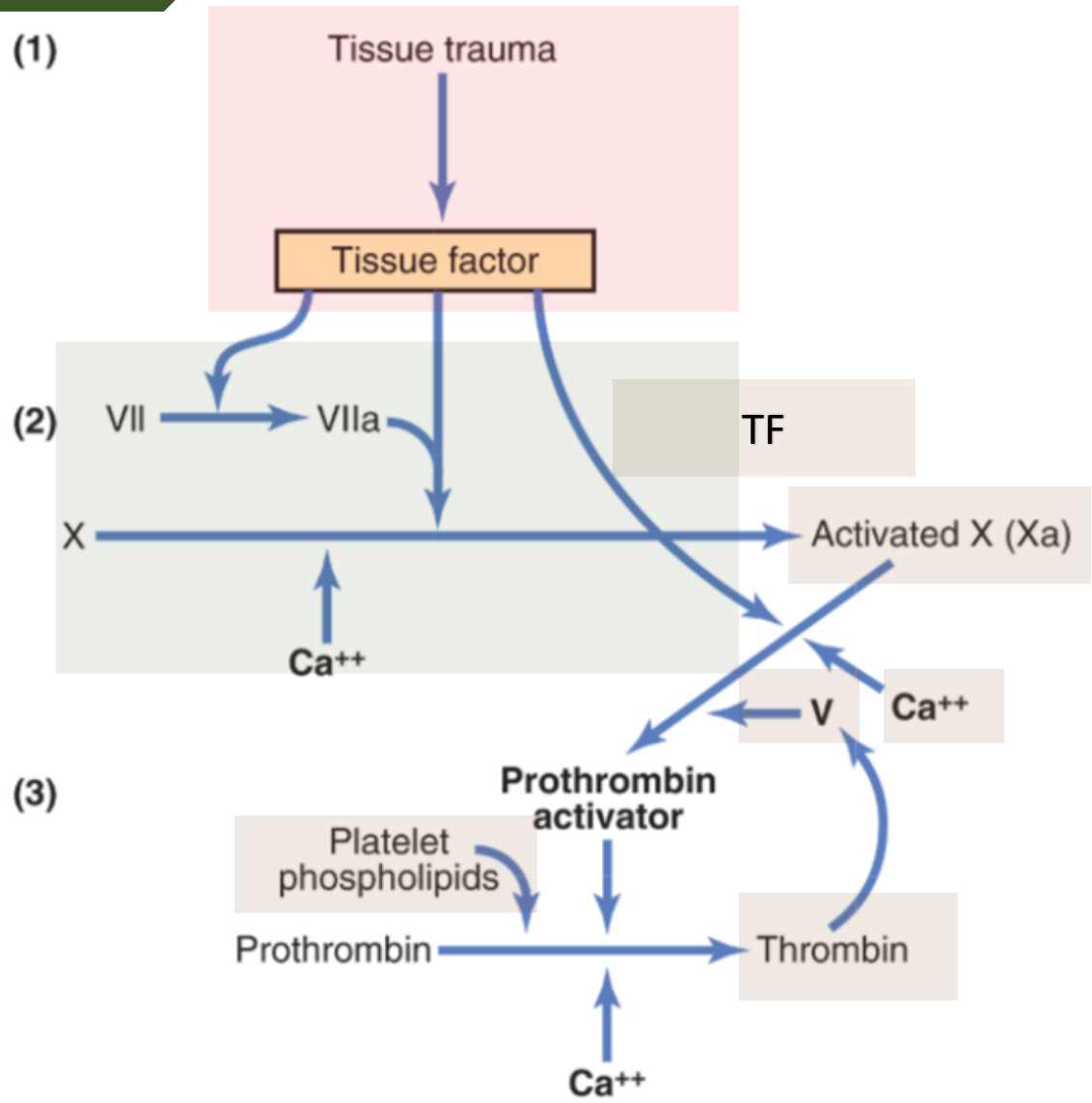
(1) by the **extrinsic pathway** that begins with trauma to the vascular wall and surrounding tissues

(2) by the **intrinsic pathway** that begins in the blood itself.



Hemostasis 3. Extrinsic pathway

1. Release of tissue factor
2. Activation of factor X—role of factor VII and tissue factor.
3. Effect of Xa to form prothrombin activator—role of factor V



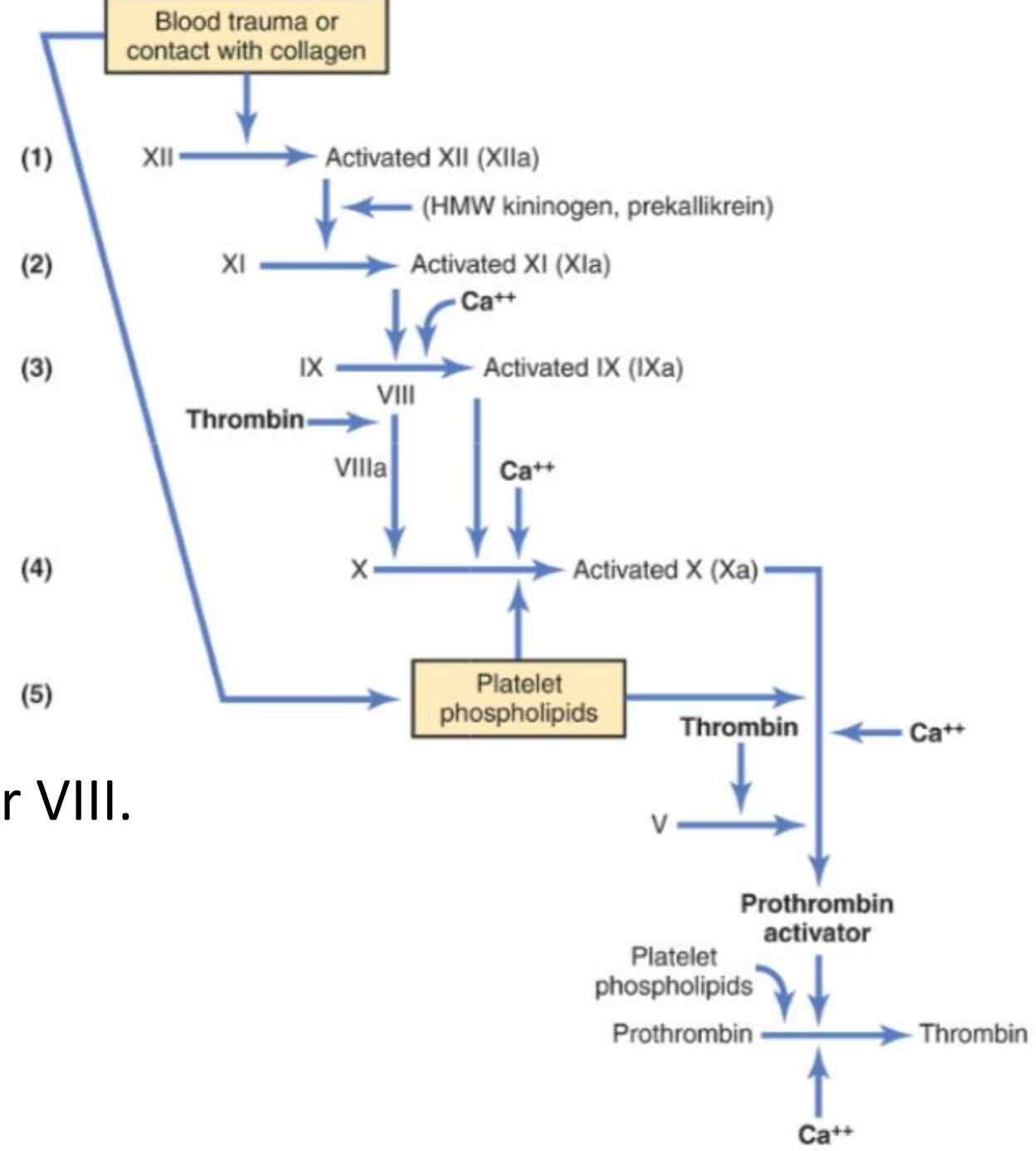
3. Intrinsic pathway

1. Blood trauma causes activation of factor XII and release of platelet phospholipids

2. Activation of factor XI

3. Activation of factor IX

4. Activation of factor X—role of factor VIII.

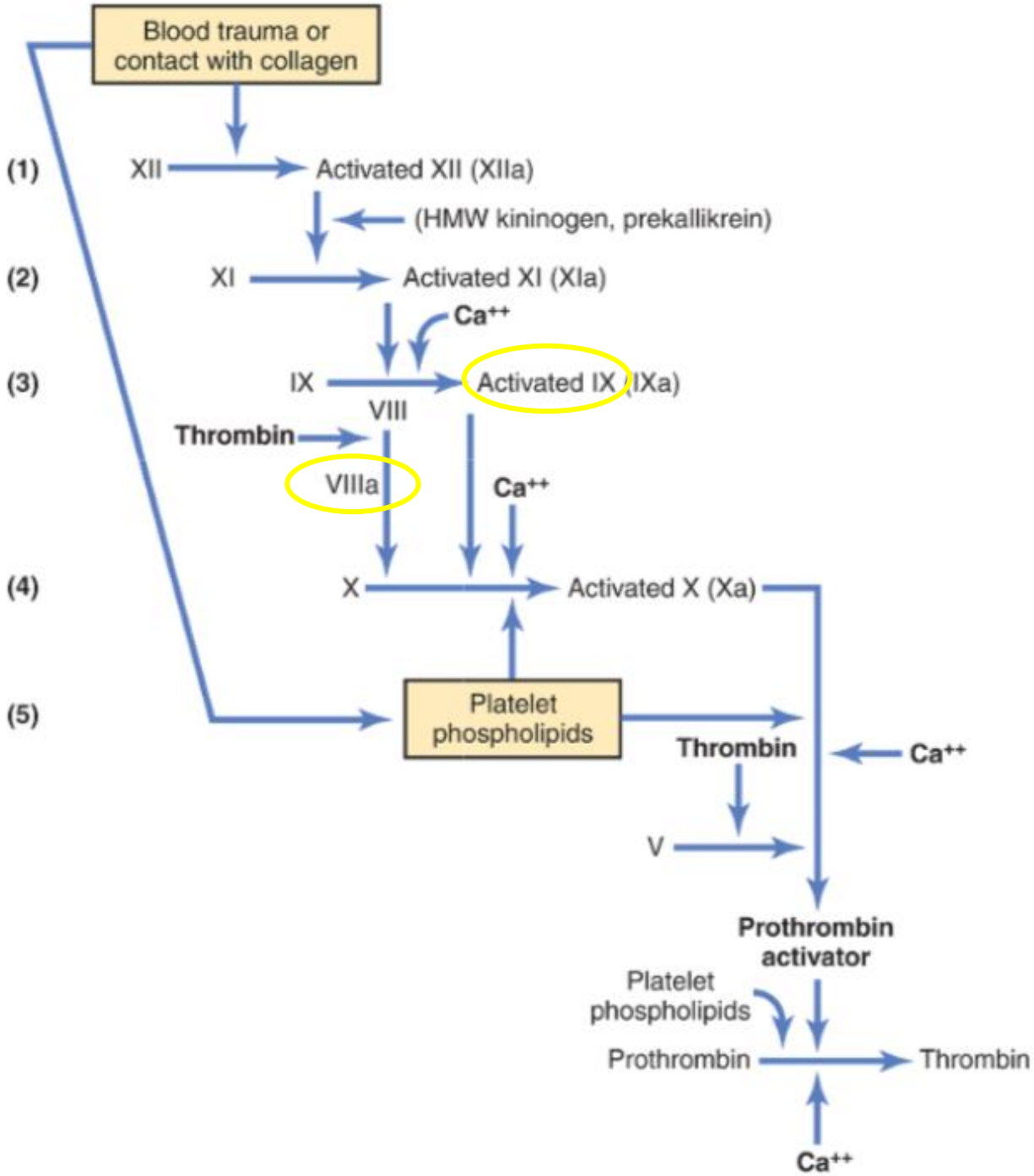


Hemostasis

3. Intrinsic pathway

hemophilia A or classic hemophilia (85%) : deficiency of Factor VIII

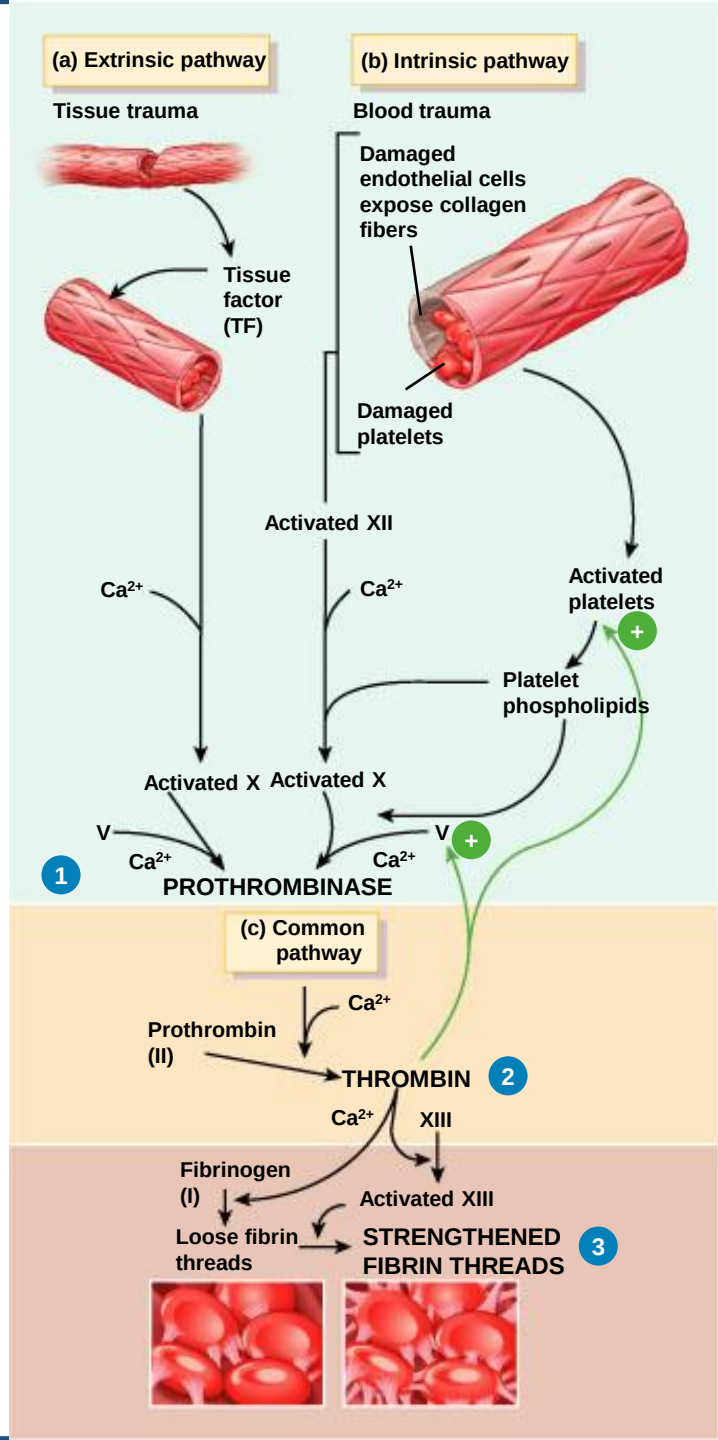
hemophilia B (15%): deficiency of Factor IX.



Hemostasis 3. Blood coagulation

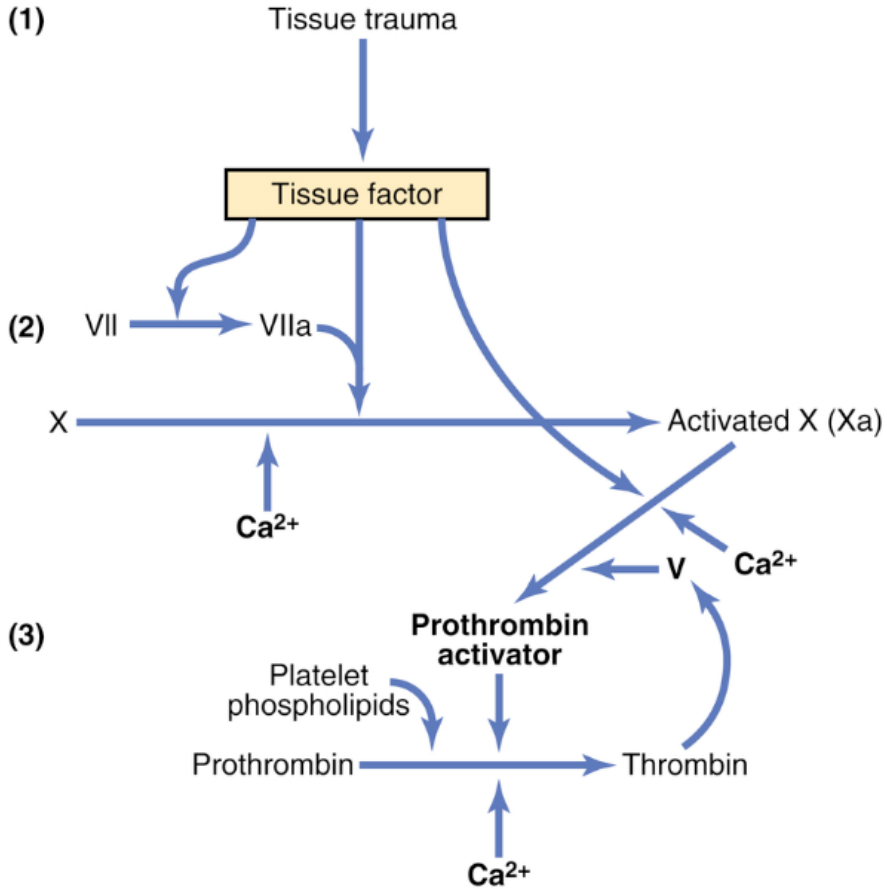
Thrombin has 2 positive feedback effects:

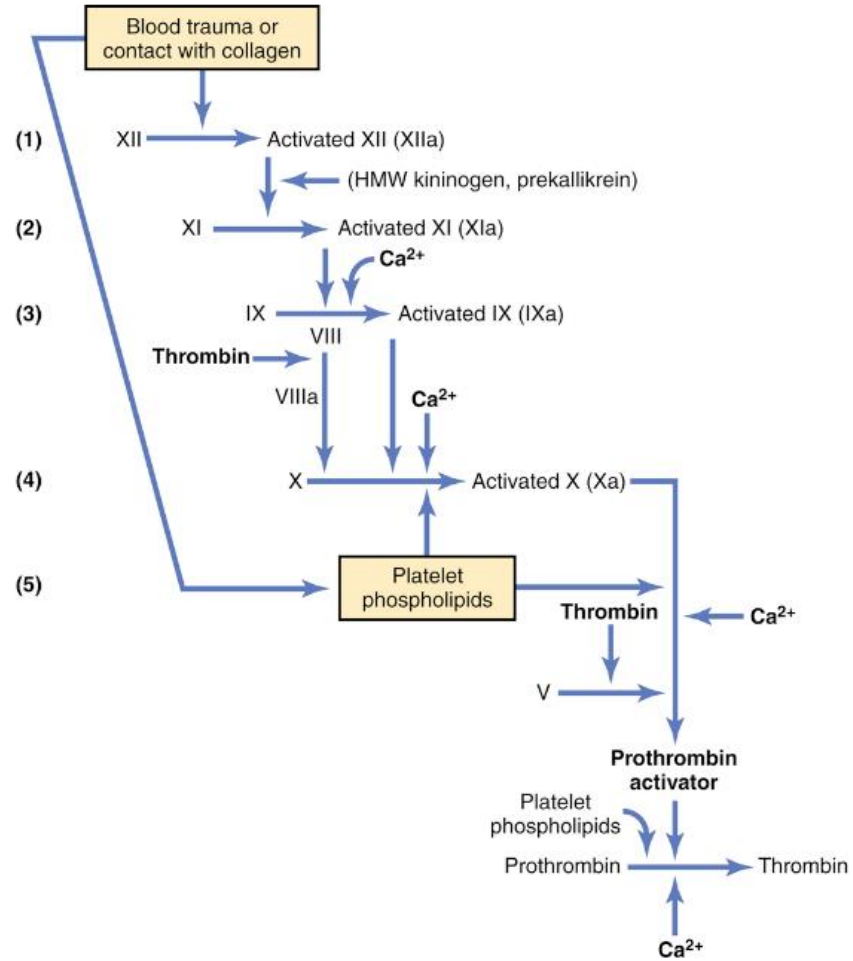
- Accelerates formation of prothrombinase (V)
- Thrombin activates platelets

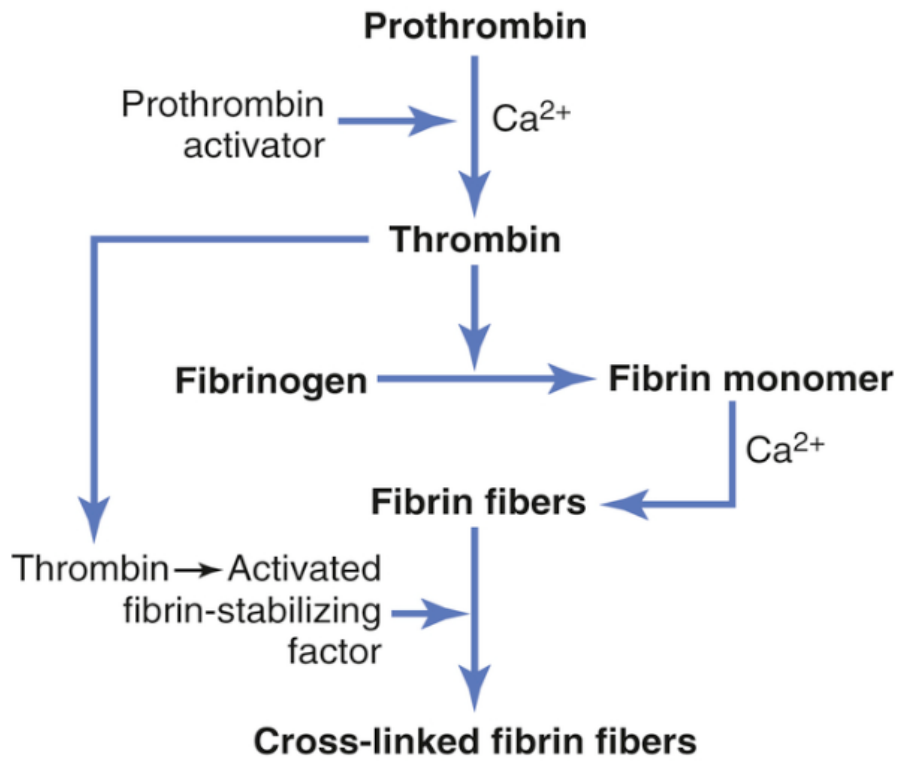


Think!

Why do we use Ethylenediaminetetraacetic acid (EDTA) tube to collect blood for CBC?


(1)
Tissue trauma
Tissue factor
(2)
VII
VIIa
X
Activated X (Xa)
Ca2+
V
Ca2+
(3)
Prothrombin activator
Platelet phospholipids
Prothrombin
Thrombin
Ca2+


Blood trauma or contact with collagen
(1)
XII
Activated XII (XIIa)
(HMW kininogen, prekallikrein)
(2)
XI
Activated XI (XIa)
Ca2+
(3)
IX
Activated IX (IXa)
VIII
Thrombin
VIIIa
Ca2+
(4)
X
Activated X (Xa)
(5)
Platelet phospholipids
Thrombin
Ca2+
V
Prothrombin activator
Platelet phospholipids
Prothrombin
Thrombin
Ca2+


Prothrombin
Prothrombin activator
Ca2+
Thrombin
Fibrinogen
Fibrin monomer
Ca2+
Fibrin fibers
Thrombin
Activated fibrin-stabilizing factor
Cross-linked fibrin fibers

Hemostasis

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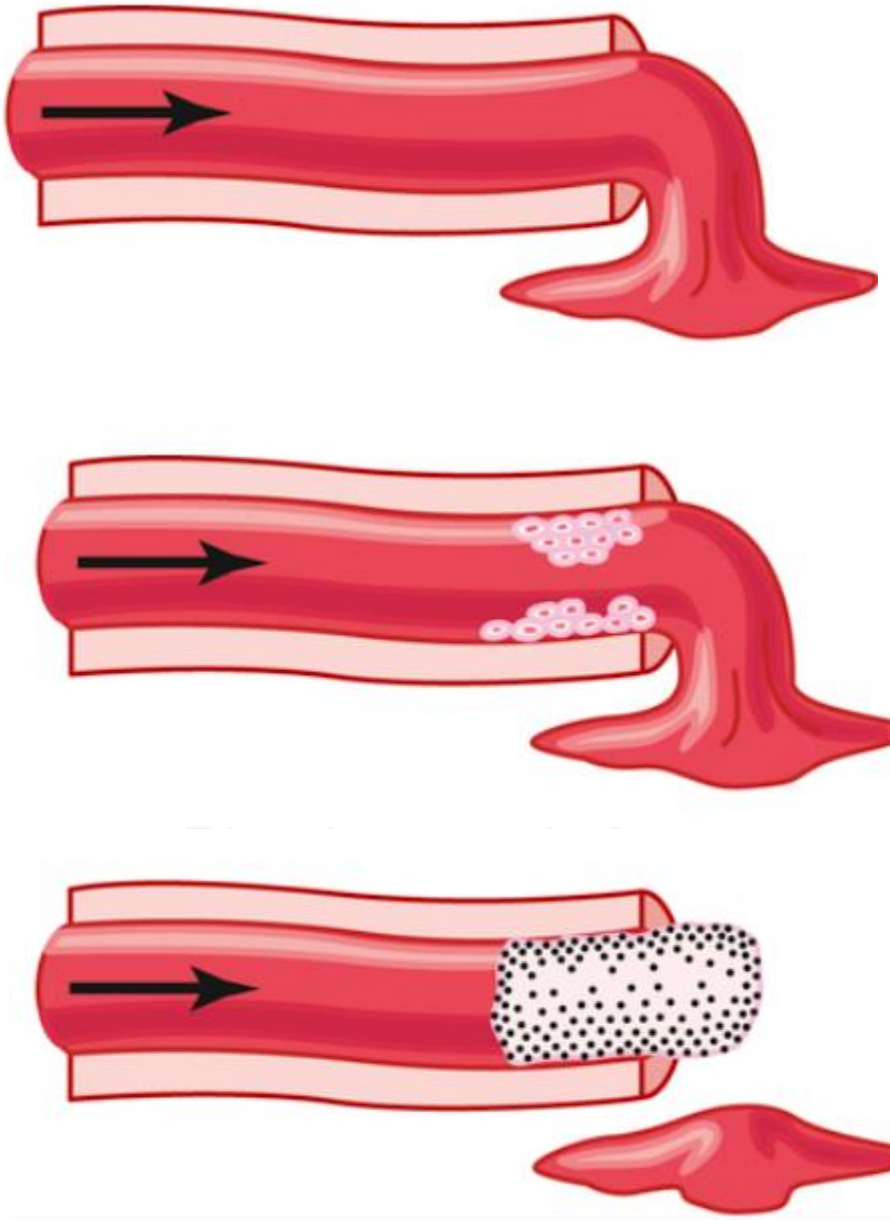


Hemostasis 4. Growth of fibrous tissue

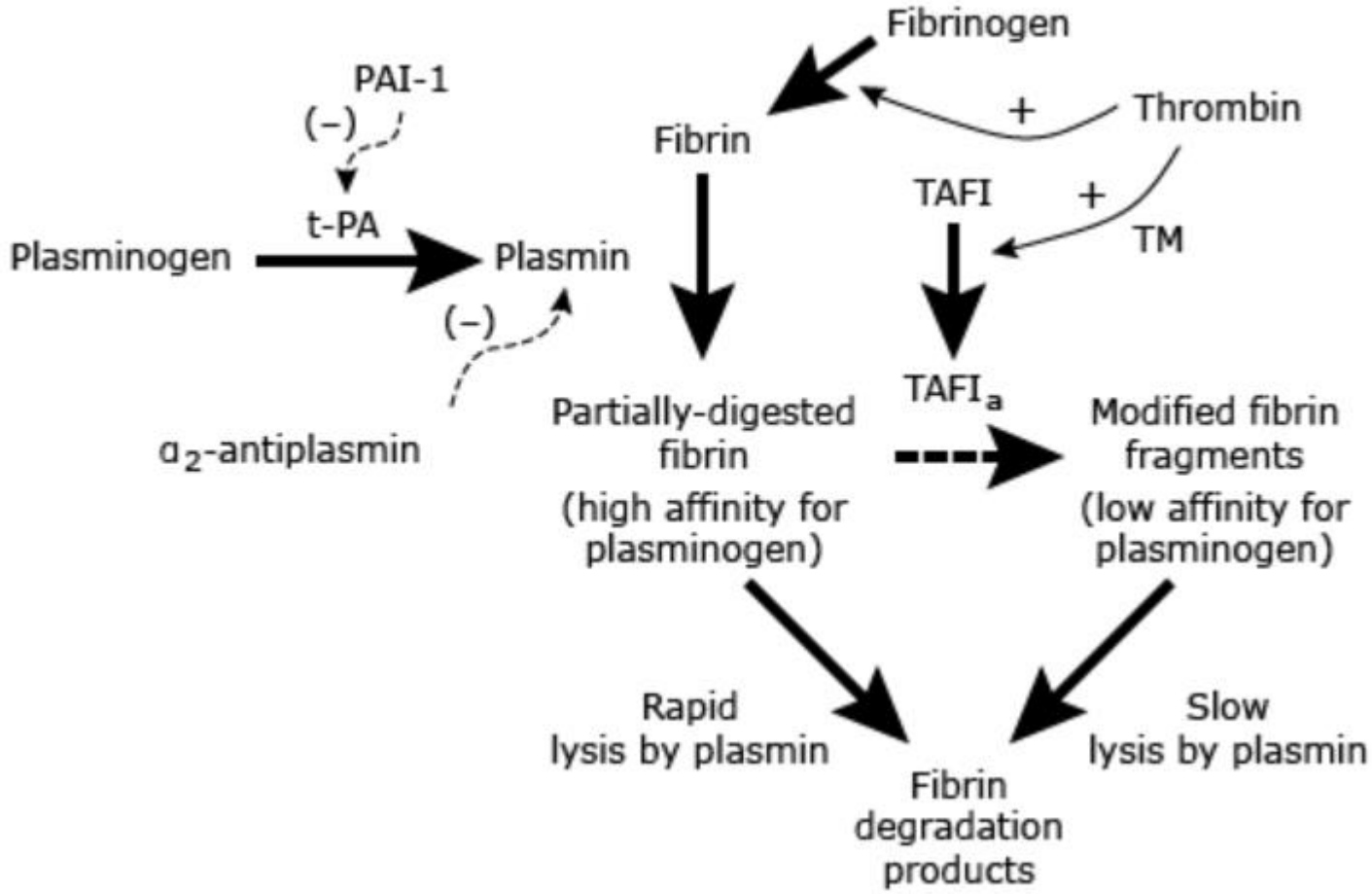
Once a blood clot has formed, it can follow one of two courses:

(1) It can become invaded by *fibroblasts,* which subsequently form connective tissue all through the clot (promoted at least partially by **growth factor** secreted by **platelets**)

(2) it can dissolve.

Hemostasis

4. Lysis of clot



Prevention — Normal Intravascular Anticoagulants

- Endothelial surface factors
- Antithrombin action of fibrin and antithrombin III.
- Heparin.

Prevention — Normal Intravascular Anticoagulants

➢ **Endothelial Surface Factors**

- 1) the *smoothness* of the endothelial cell surface
- 2) a layer of **glycocalyx** on the endothelium
- 3) a protein bound with the endothelial membrane, **thrombomodulin,** which binds **thrombin**.
- the **thrombomodulin-thrombin** complex also activates a plasma **protein C**, that acts as an anticoagulant by **inactivating** activated **Factors V and VIII.**
- 4) Intact endothelial cells also produce other substances such **a prostacyclin and nitric oxide (NO)** that inhibit **platelet aggregation** and initiation of blood clotting

➢**Antithrombin Action of Fibrin and Antithrombin III.**

- Among the most important anticoagulants in the blood are those that remove thrombin from the blood.

(1) the **fibrin fibers** that are formed during the process of clotting (85 to 90%)

(2) The thrombin that does not adsorb to the fibrin fibers soon combines with **antithrombin III.** (an alpha-globulin)

Prevention — Normal Intravascular Anticoagulants

➢ **Heparin**

- Highly negatively charged conjugated polysaccharide
- Powerful anticoagulant, but its concentration in the blood is normally low.
- Widely used as a pharmacological agent.
- Increases effectiveness of antithrombin III.
- Inhibits thrombin, activated factors xII, xI, x, and Ix.
- Produced in basophil and mast cells.

Prevention — Outside body Anticoagulants

- When blood is collected in a glass test tube normally clots in about 6 minutes.
- **Siliconized containers** often does not clot for 1 hour or more. silicone prevents contact **activation of platelets and Factor XII.**
- **Heparin** → when blood must be passed through a heart-lung machine or artificial kidney machine and then back into the person.
- **Soluble oxalate, citrate ion**→ decreases the ionic calcium level → blood coagulation is blocked

Thromboembolic Conditions → Causes

- A thrombus → an abnormal clot that develops in a blood vessel.
- An embolus → freely flowing clots.
- Emboli that originate in large arteries or in the left side of the heart → brain, kidneys, or elsewhere.
- Emboli that originate in the venous system or in the right side of the → lungs (pulmonary embolism).

- **Cause of Thromboembolic Conditions**

(1) Any roughened endothelial surface of a vessel—as may be caused by arteriosclerosis, infection, or trauma—is likely to initiate the clotting process.

(2) Blood often clots when it flows very slowly through blood vessels, where small quantities of thrombin and other procoagulants are always being formed.

- **Disseminated Intravascular Coagulation**
- This often results from the presence of **large amounts** of **traumatized tissue** in the body that releases **great quantities of tissue factor** into the blood.
- **Septicemia**, in which either circulating bacteria or bacterial toxin
- Plugging of small peripheral vessels greatly diminishes delivery of oxygen and other nutrients to the tissues.
- Bleeding → The reason for this is that so many of the clotting factors are removed by the widespread clotting

Think!

There is genetically engineered tissue plasminogen activator (t-PA) available.

When can you use tPA ?

Self Reading!

Prothrombin time [**PT**]
Activated thromboplastin time [**aptt**]