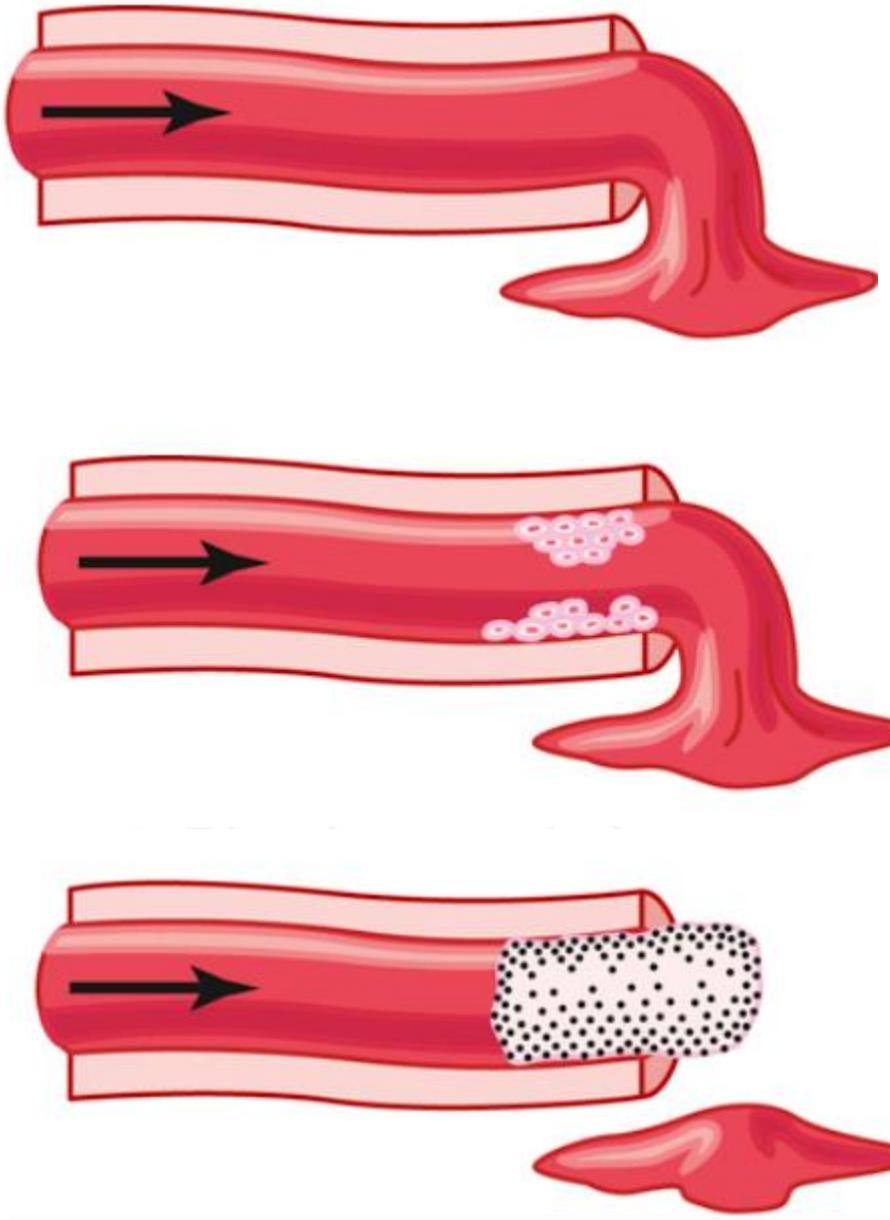
Hemostasis

Events of hemostasis

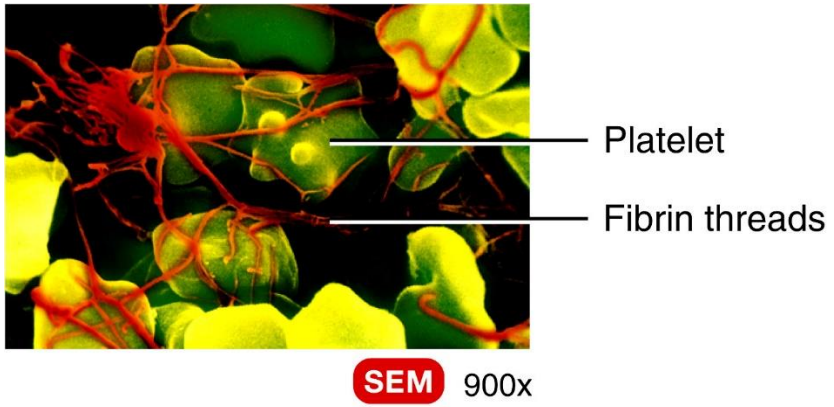
Hemostasis means prevention of blood loss and includes the following events:

(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



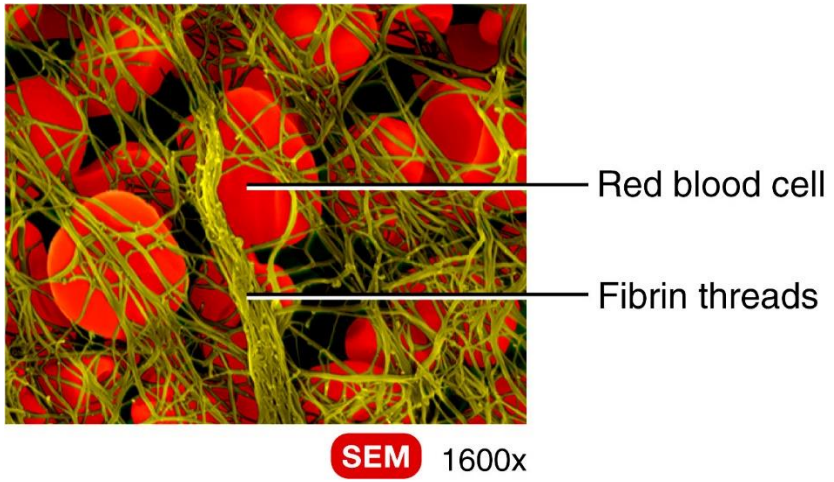
Hemostasis Blood clot

- 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

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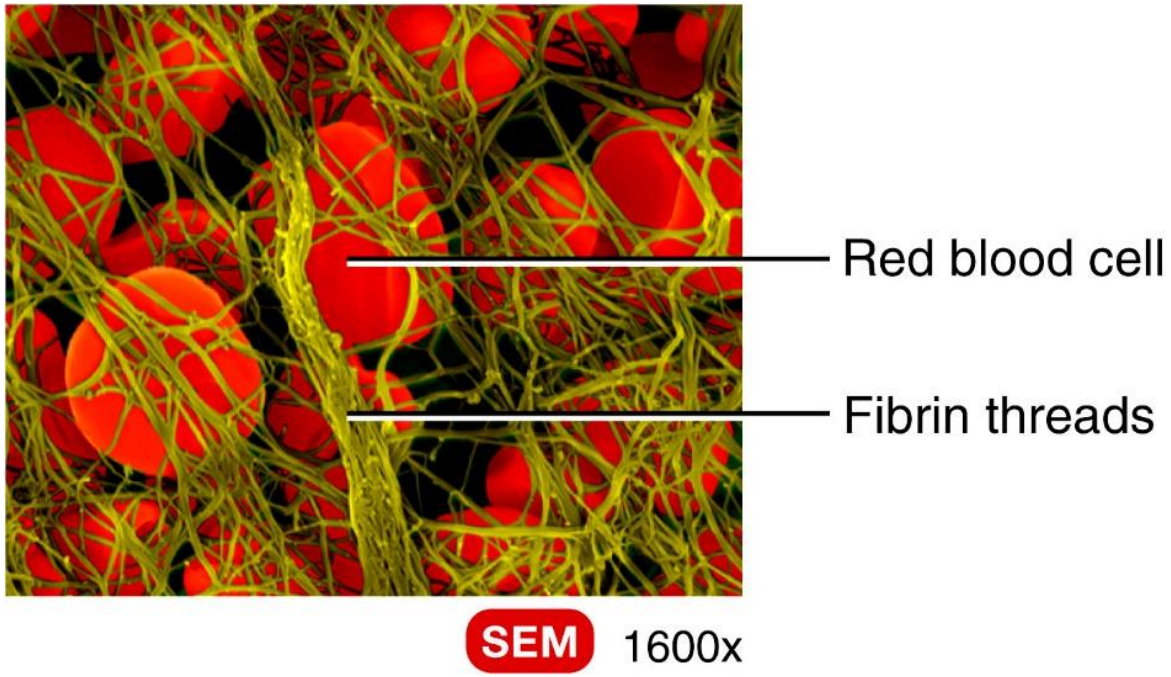
(d) Red blood cells trapped in fibrin threads

Figure 19.10d Tortora - PAP 12/e
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Hemostasis 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**.



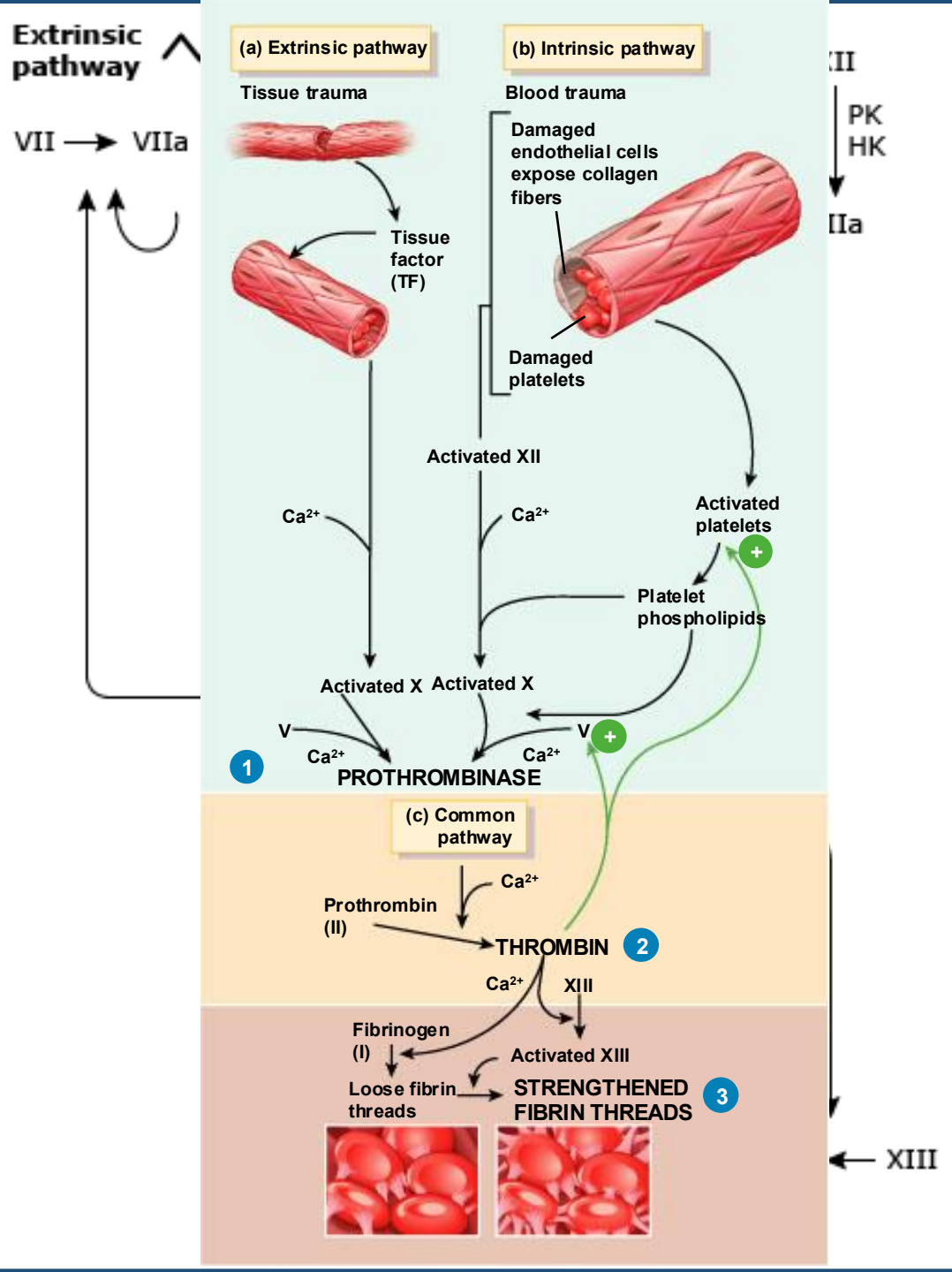
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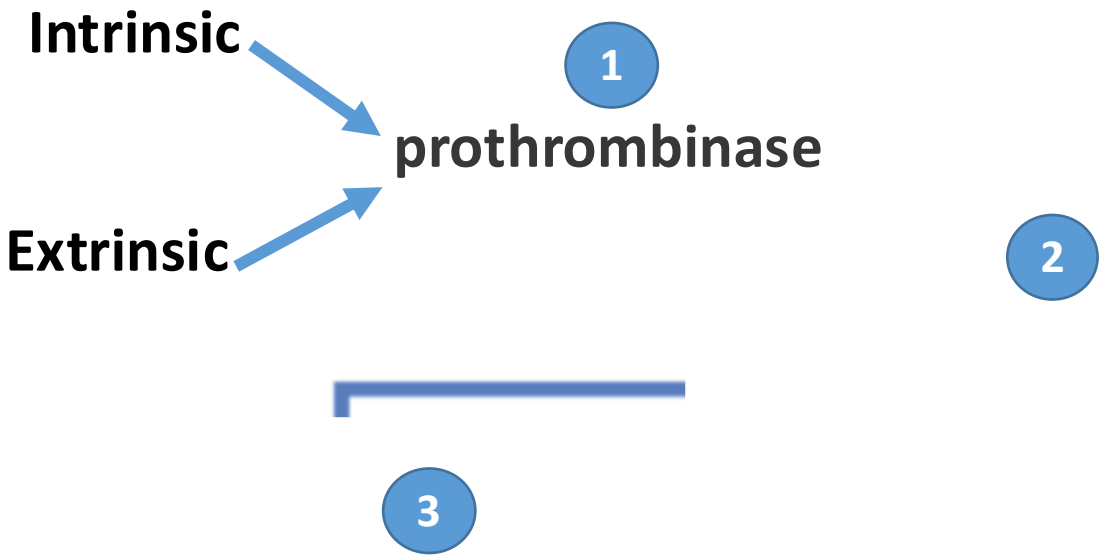
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Hemostasis

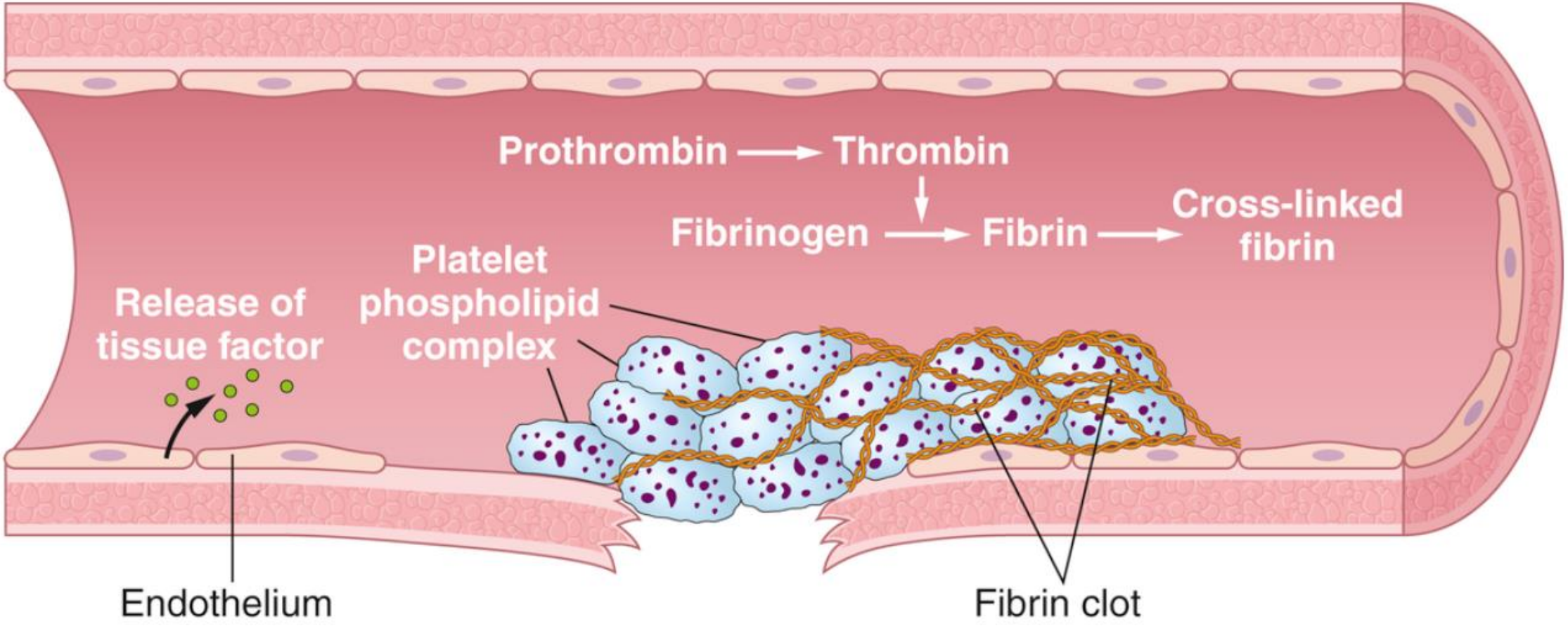
Blood coagulation

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
2
3

Hemostasis > Common pathway



Hemostasis — 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.

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

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

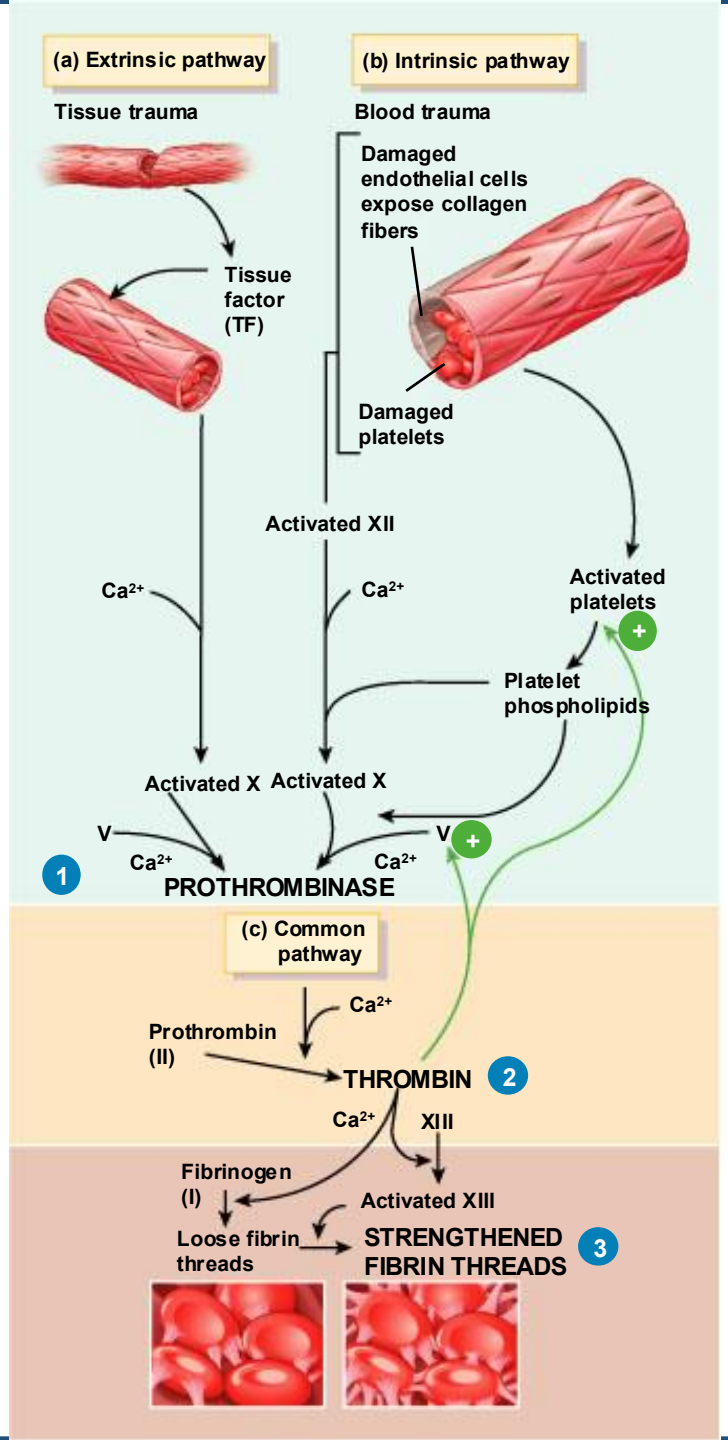
- Fibrinogen is a high-molecular-weight protein that occurs in the **plasma.**
- Fibrinogen is **formed in the liver.**
- Because of its **large molecular size**, little fibrinogen normally leaks from the blood vessels into the interstitial fluids, and because fibrinogen is one of the essential factors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

Hemostasis — Blood coagulation

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

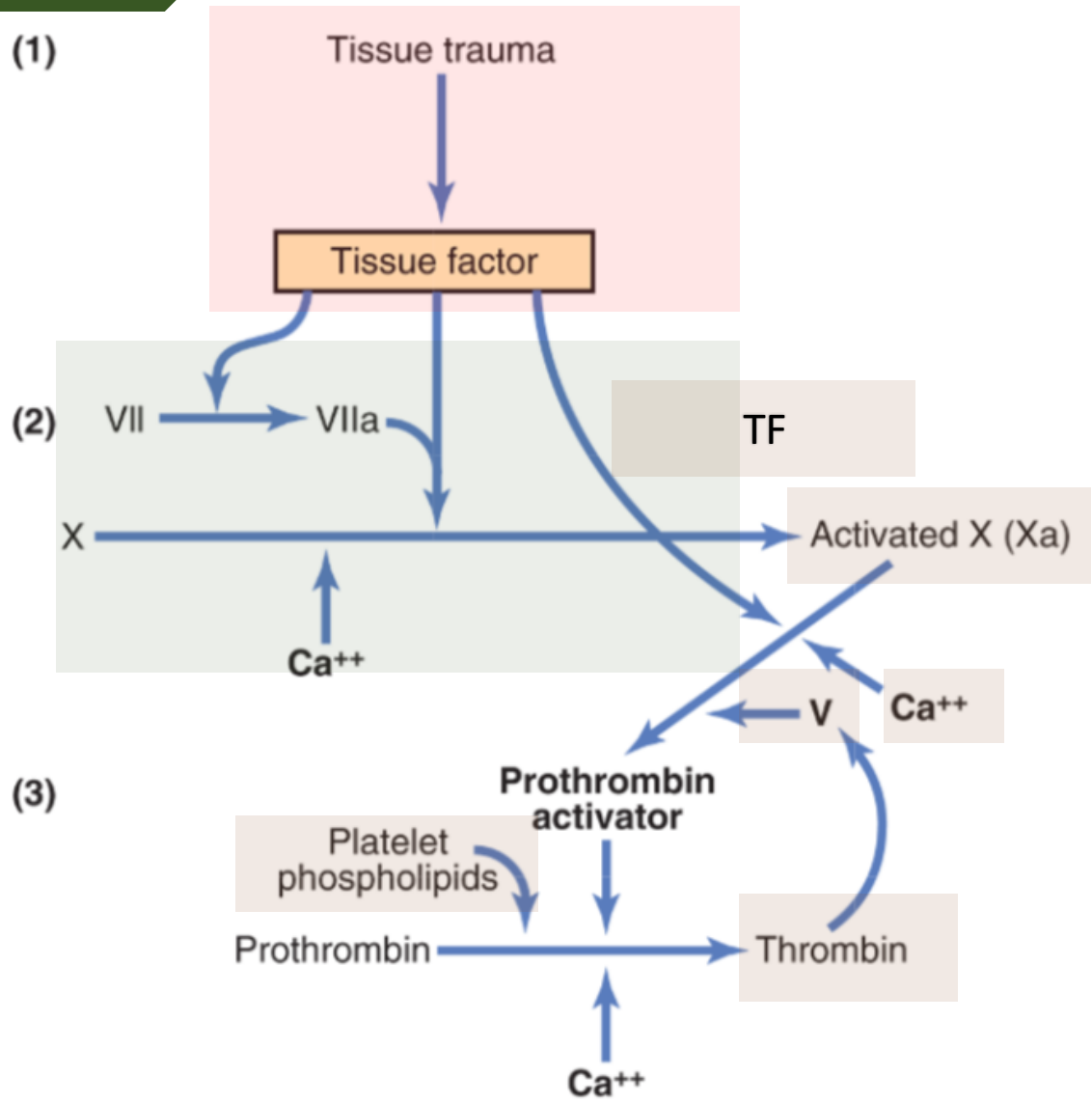
(1) by the **extrinsic pathway** that begins with trauma to the vascular wall and surrounding tissues

(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



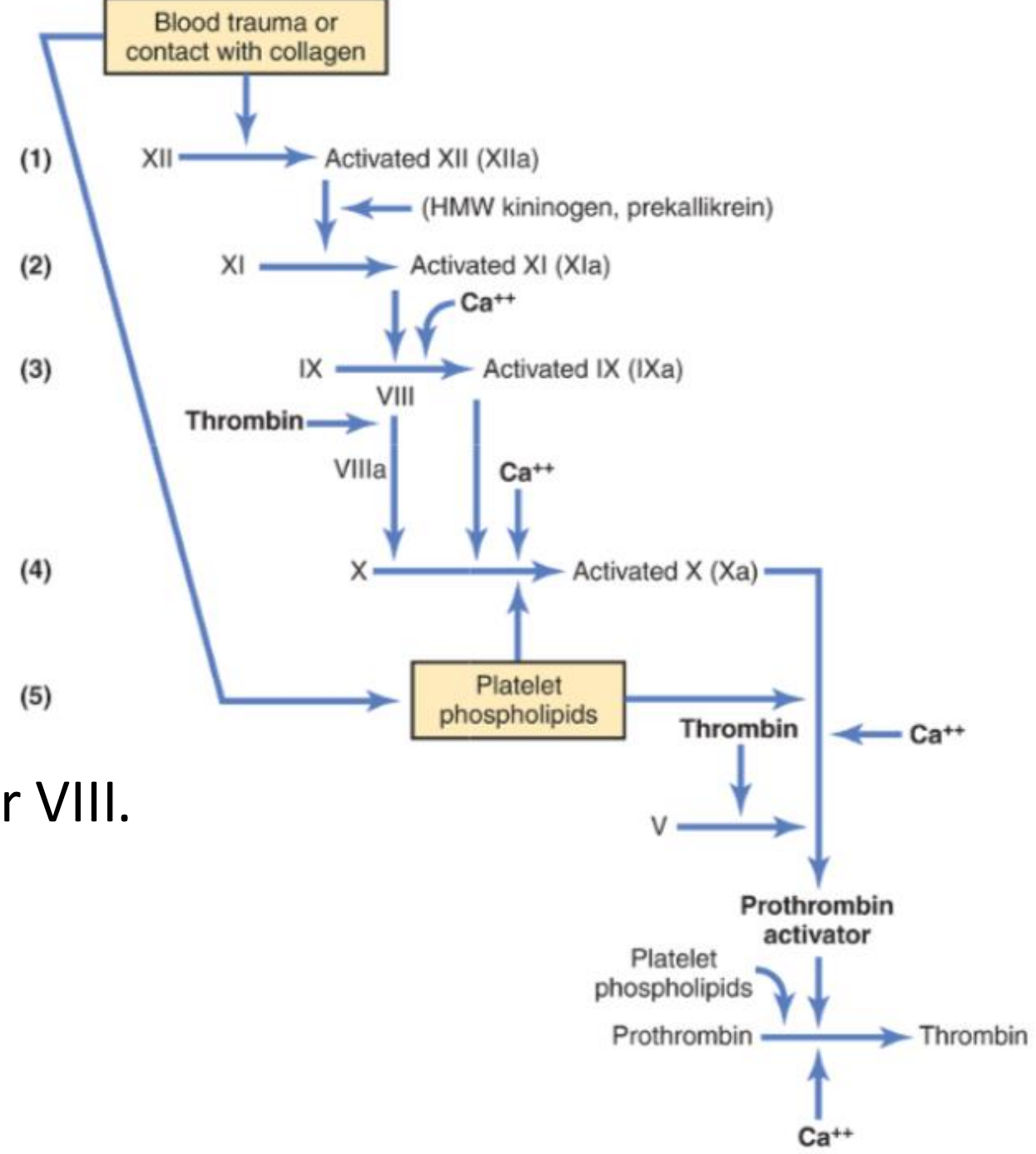
3. Intrinsic pathway

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.

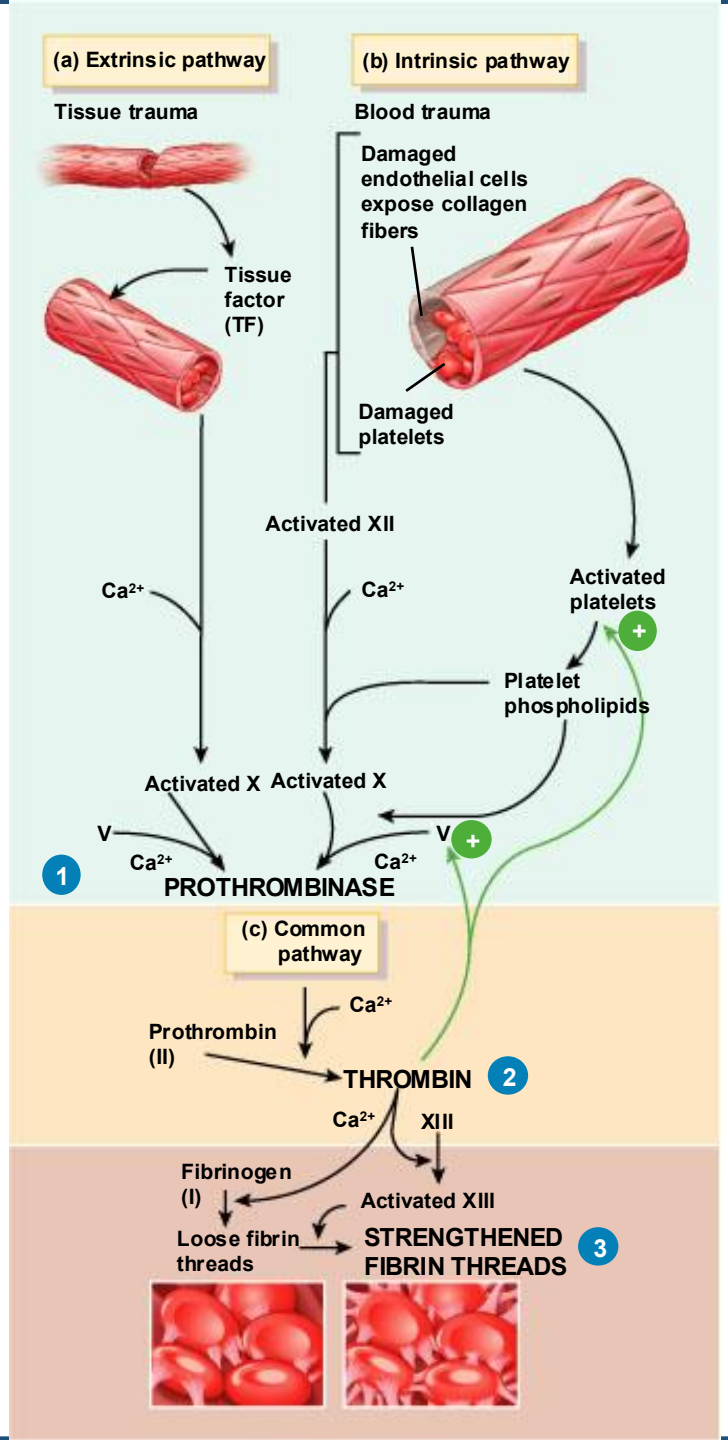


Hemostasis

Thrombin

Thrombin has 2 positive feedback effects:

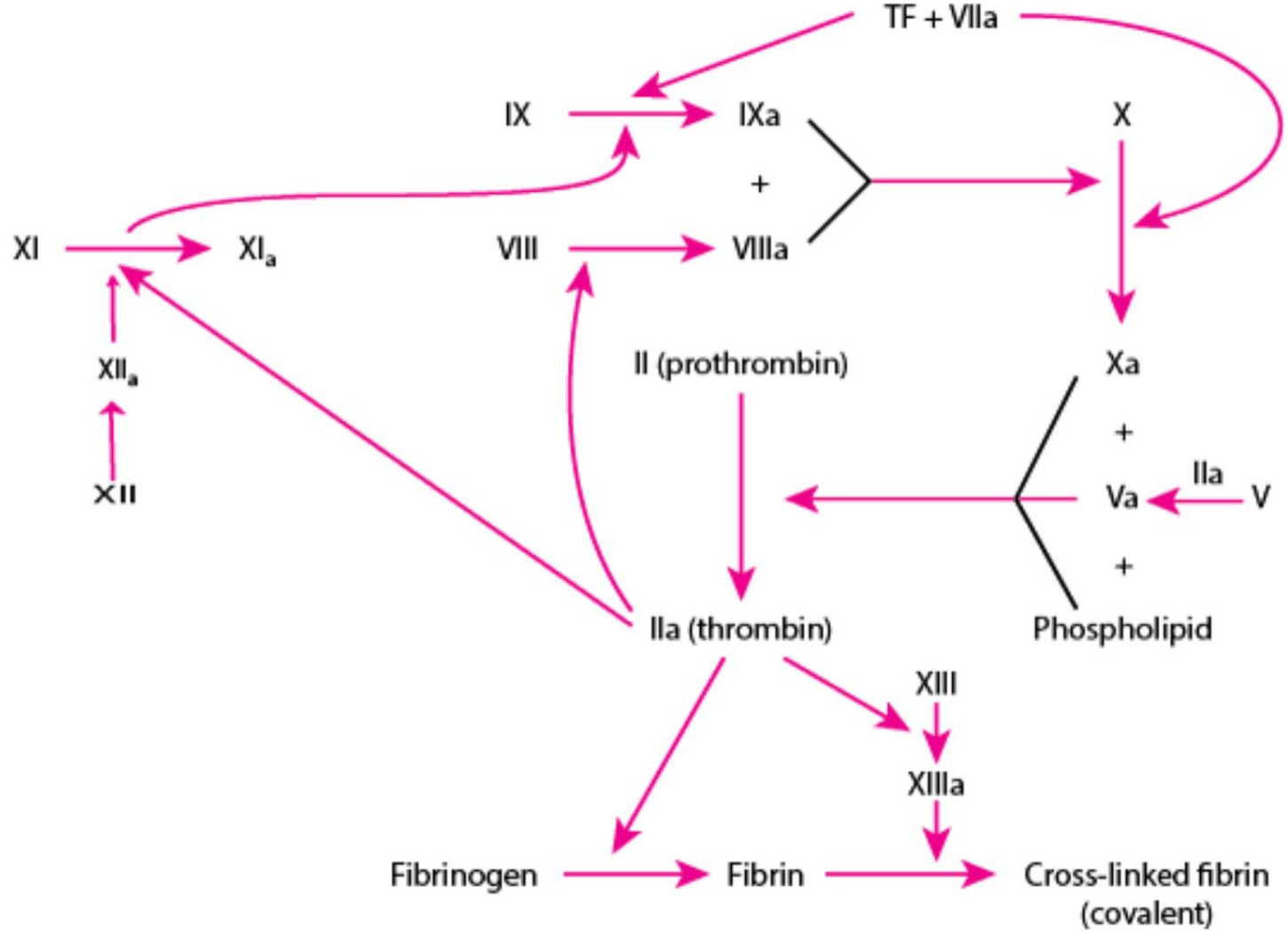
- Accelerates formation of prothrombinase (V)
- Thrombin activates platelets



Think!

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



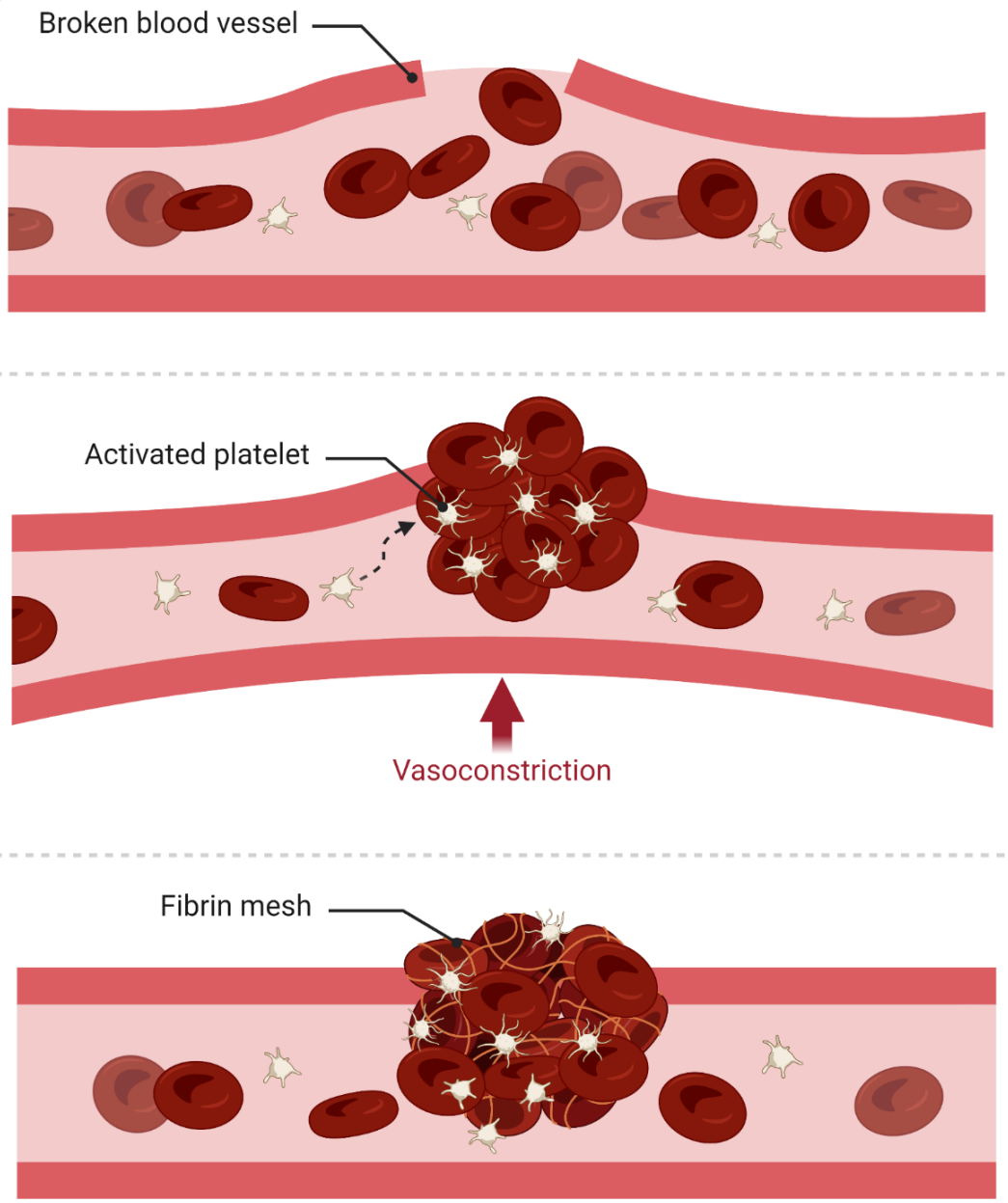

TF + VIIa
IX
IXa
+
X
XI
XIa
VIII
VIIIa
XIIa
XII
II (prothrombin)
Xa
+
IIa
Va
V
+
IIa (thrombin)
Phospholipid
XIII
XIIIa
Fibrinogen
Fibrin
Cross-linked fibrin
(covalent)

Hemostasis — 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.

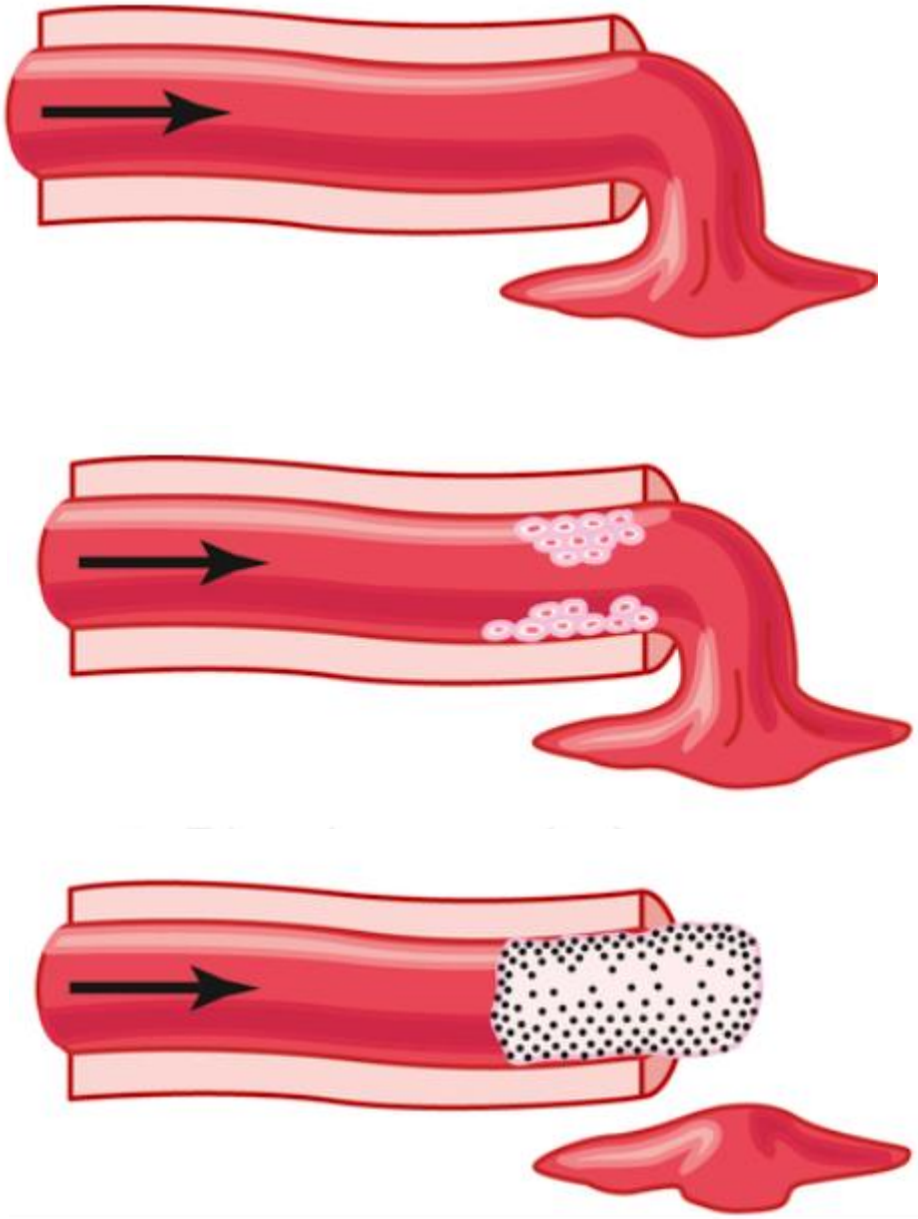


Hemostasis

Events of hemostasis

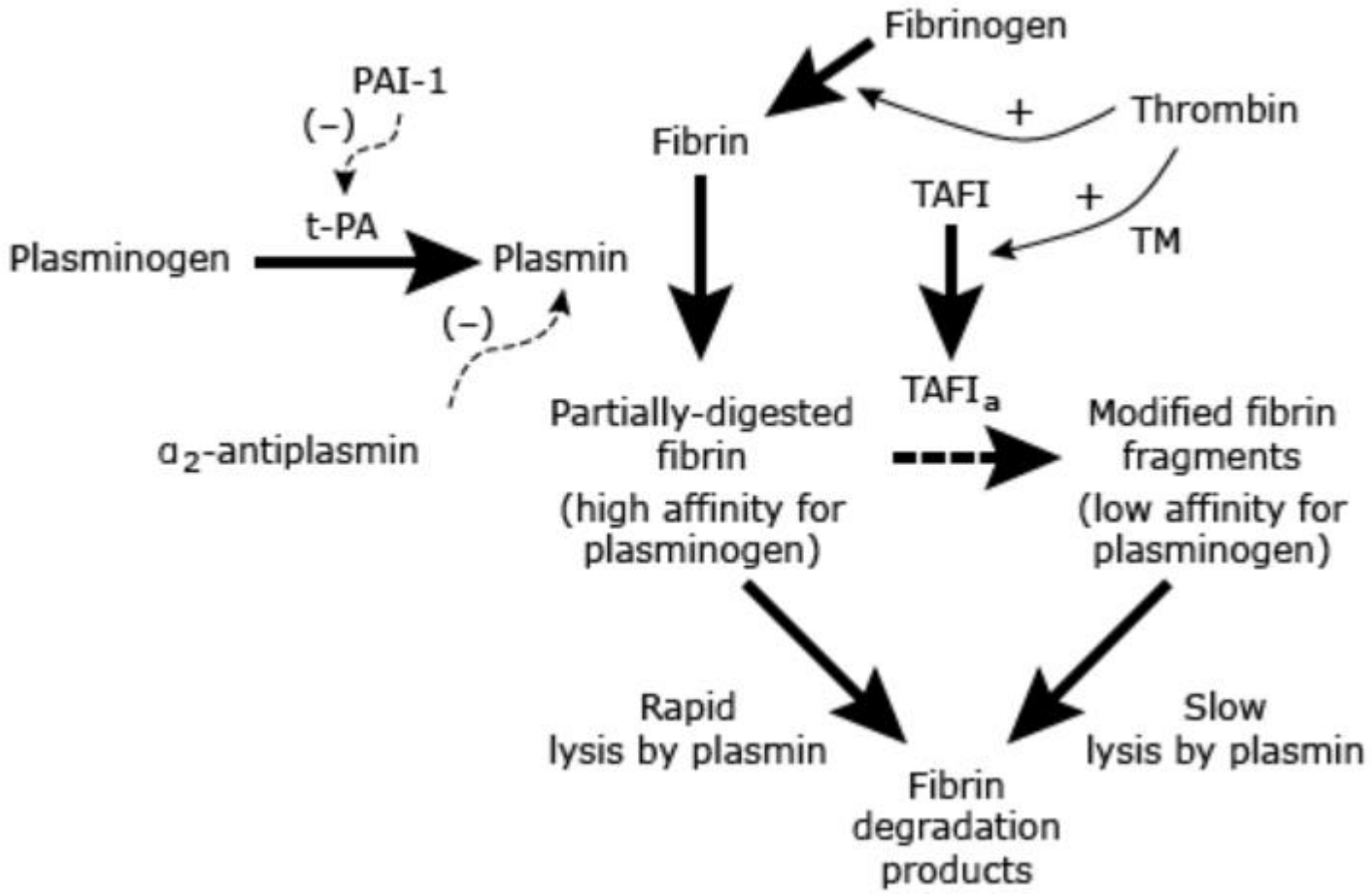
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(4) Fibrous organization or dissolution of the blood clot



Hemostasis

Dissolution of clot



Think!

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

When can you use tPA ?

Fibrous organiazation

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

Prevention — Normal Intravascular Anticoagulants

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

Prevention 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**, with protein S as a cofactor, 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

Prevention

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 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 Anticoagulants (Outside body)

- 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

What happens when different components fail?

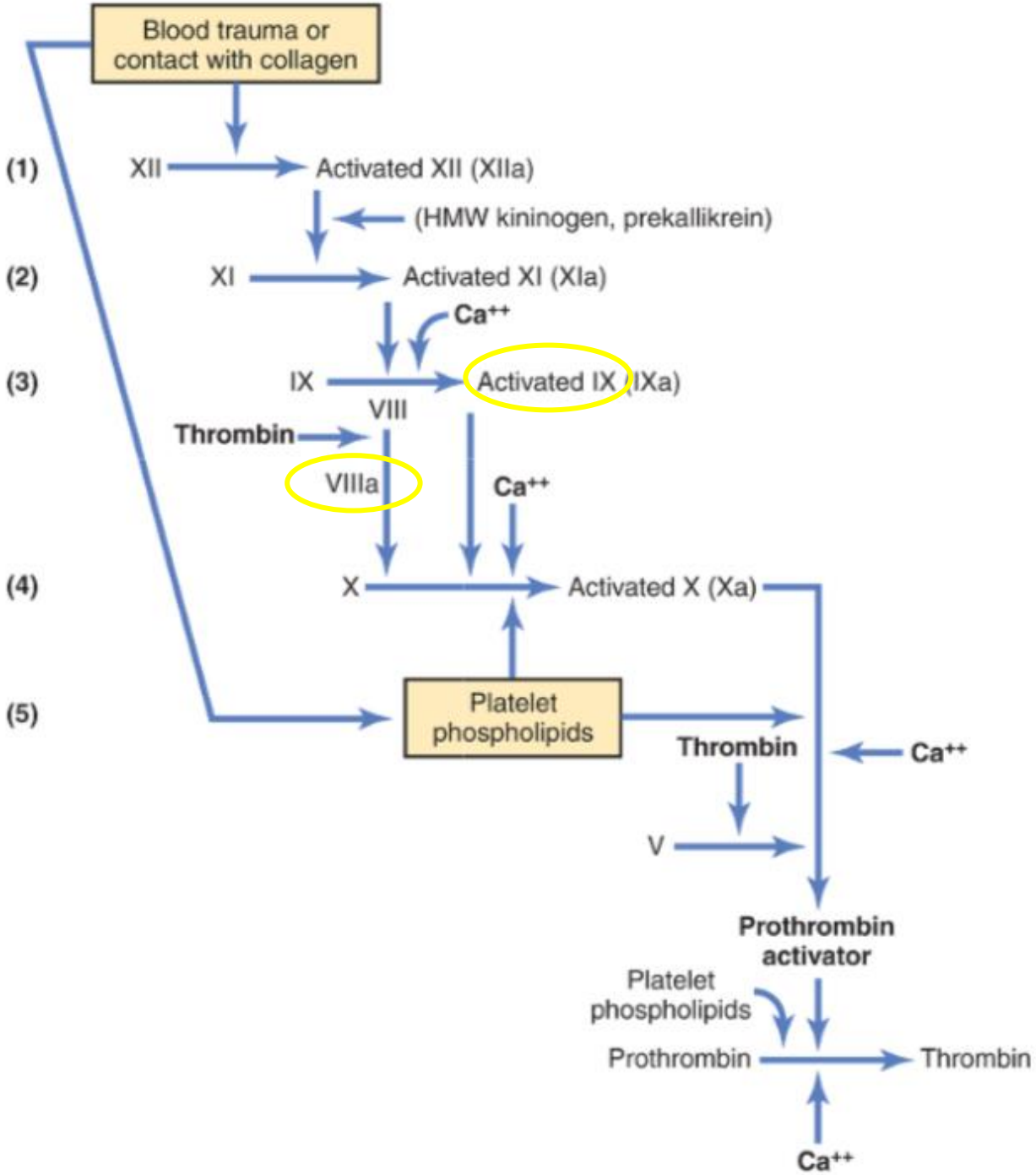
- If platelet number or function is impaired →

  the rapid seal at small vascular injuries becomes less effective. This commonly produces **mucocutaneous bleeding**: petechiae, nosebleeds, gingival bleeding, or heavy menstrual bleeding.

Hemostasis

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

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



What happens when different components fail?

- If platelet number or function is impaired →

  the rapid seal at small vascular injuries becomes less effective. This commonly produces **mucocutaneous bleeding**: petechiae, nosebleeds, gingival bleeding, or heavy menstrual bleeding.

- If coagulation factors are deficient→

  the initial platelet plug may form, but fibrin reinforcement is impaired. Severe factor deficiencies more typically produce **deep bleeding**, including muscle hematomas and bleeding into joints

PT and aPTT

Time to form a fibrin clot in citrated, platelet-poor plasma

	PT	aPTT (often called PTT)
Full name	Prothrombin time	Activated partial thromboplastin time
Reagents added	Tissue factor, phospholipid + calcium	Contact activator, phospholipid + calcium
Pathways assessed	Extrinsic + common	Intrinsic + common
Factors assessed	VII + X, V, II, I	XII, XI, IX, VIII + X, V, II, I
Typical prolongation	Factor VII deficiency	Hemophilia A or B
Range	12-14 seconds	25-30 seconds