Pathology

Subject : Hemodynamics lecture 3 +4

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Audio 3

Lec no : lec-18-

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وَقُل رَّبِّ زِدْنِي عِلْمًا

* hemostasis هي عملية تكون كتلة صلبة من الدم الهدف منها هو سد ثقب في Blood vessel لحين ترميم ال (BV) ثم يحدث تدويب لها Thrombus

* تتكون ال hemostasis من ① fibrin ② platlets

* حضرت شرح د حمزه حداد
* حسيت احسن الملخص

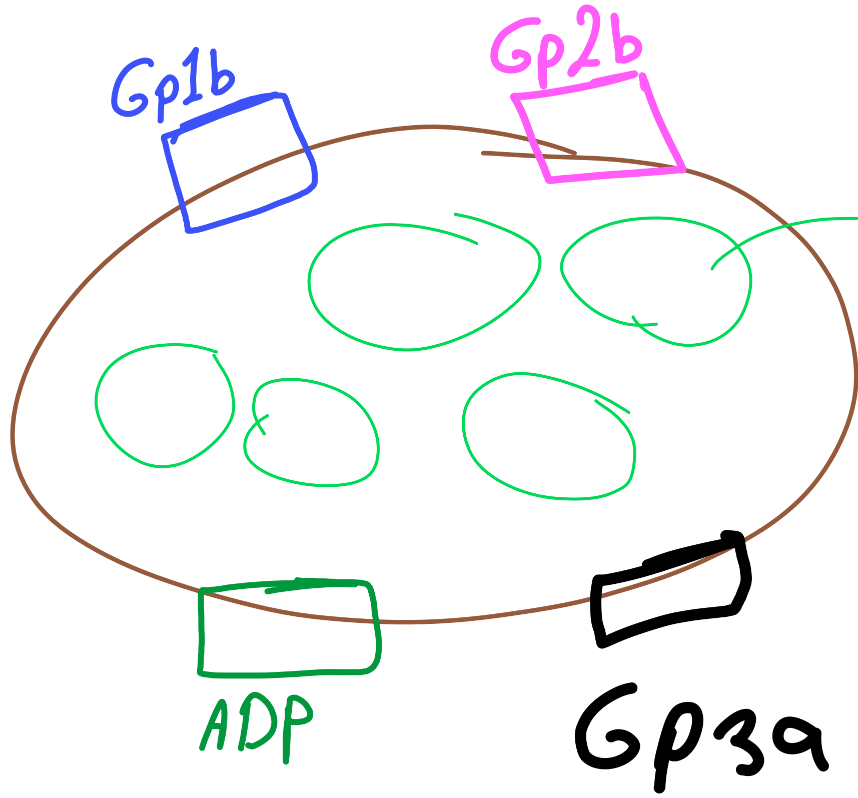
Hemostasis

Transient (V C)
مسؤول عنها Blood vessels

② Primary hemostasis
مسؤول عنها ال platlets

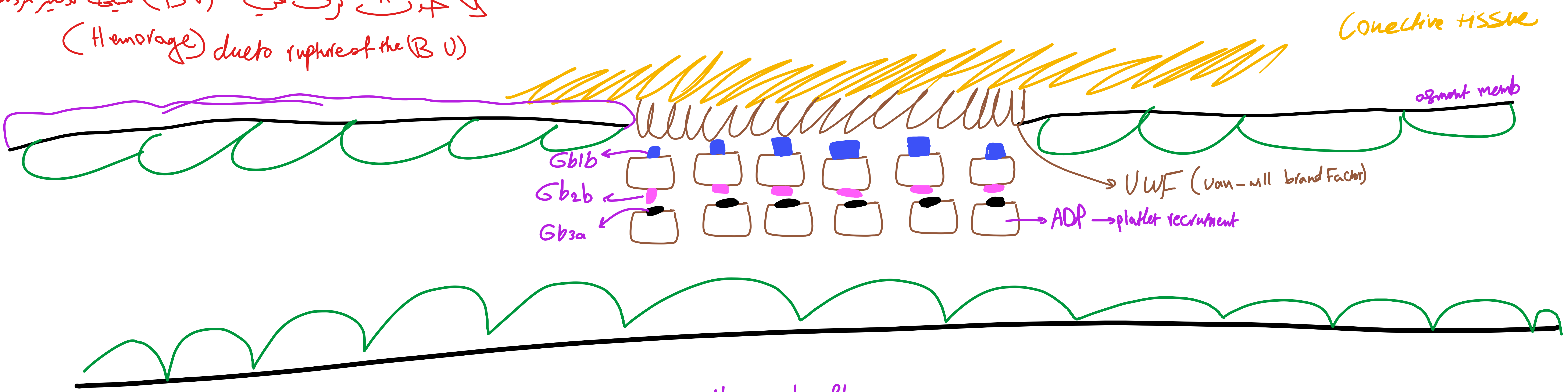
③ secondary hemostasis
مسؤول عنها بروتينات تسمى clotting factor

* Structure of platlets



Granules consist of ① fibrinogen ② PDGV (platlet derived growth factor) ③ Ca^{+2} ④ PL (phospho lipids) ⑤ Seratonin ⑥ TXA_2 ⑦ ADP

لا يحدث نزف في (BV) نتيجة تدمير جرحه
(Hemorage) due to rupture of the (BV)



① Transient (VC) تقليل تدفق الدم للمكان
→ Neuronal reflex
→ endothelin → from damaged endothelial cells

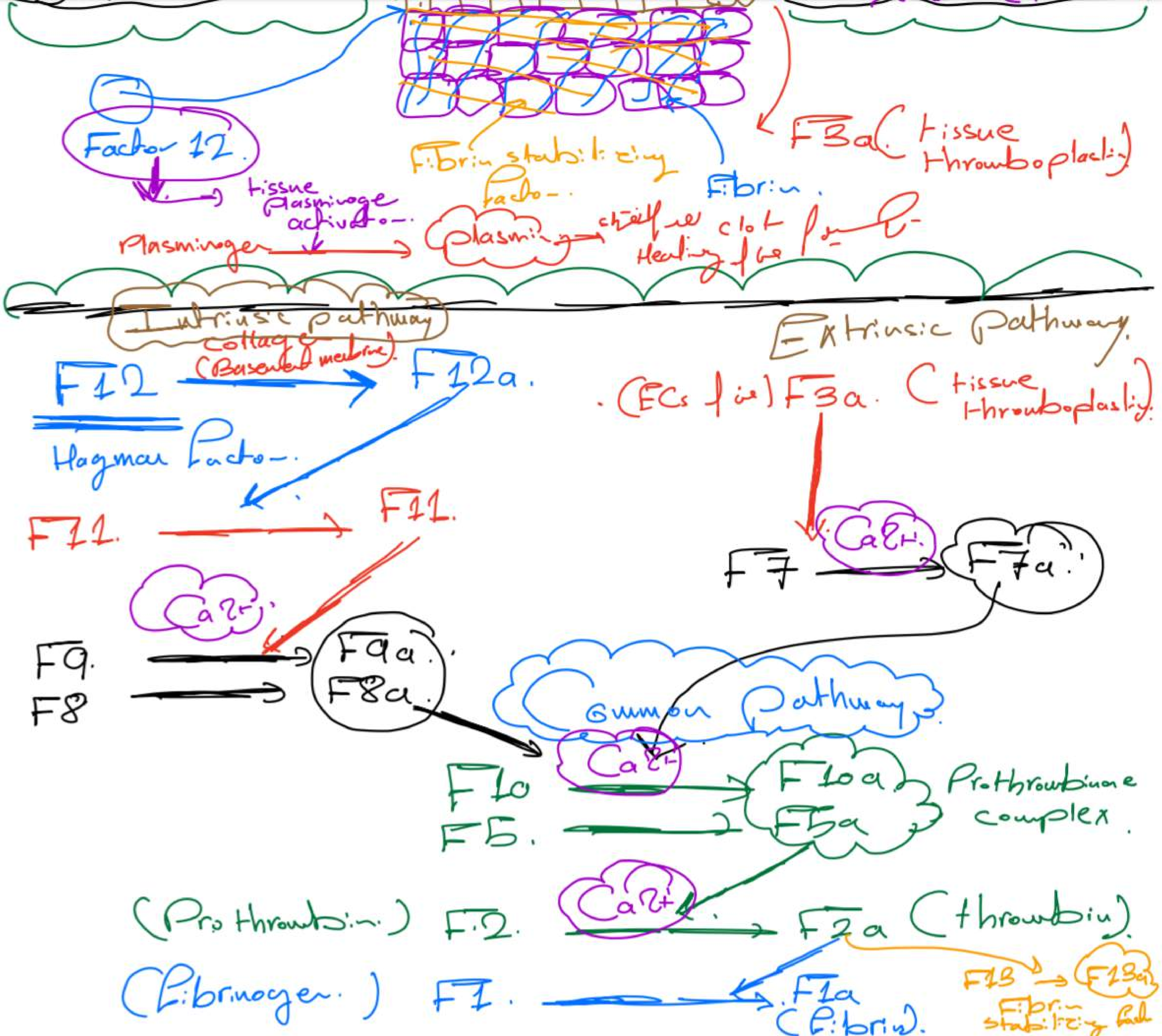
② Primary hemostasis (A) platlet adhesion Between platlets (Gp1b) → CT VWF (B) platlet activation (degranulation)
- TXA_2 → VC
- seratonin → VC
- ADP → platlet recrutment
- fibrinogen
- Ca^{+2}/PL دور في secondary hemostasis

(C) platlet aggregation Gb2b → Gb3a حرس يعمل & fibrinogen يأتي ال

(D) Formation of platlet plug (BV) من كتلة صغيرة من (platlets) هدفها اغلاق مؤقت للتشقق

③ Secondary hemostasis (Inactive) هدفها تقوية ال (platlet plug) وسؤول بها بروتينات تسمى clotting factor يتم انتاجهم من الكبد يتواجدوا داخل البلازما على شكل & يطلق عليهم اسم (Zymogens) & عددهم (13)

* نهاية secondary hemostasis يتم تكوين (fibrin clot) ← platlets, fibrin, fibrin stabilizing factor


Factor 12.
tissue plasminogen activator
Plasminogen
Plasmin
clot
Fibrin stabilizing factor
Fibrin.
F3a (tissue thromboplastin)
Intrinsic pathway
collagen (Basement membrane)
F12
F12a.
Hagman Factor.
F11.
F11.
Ca2+
F9.
F8
F9a.
F8a.
Extrinsic pathway.
(ECs) F3a. (tissue thromboplastin)
F7
F7a.
Ca2+
Common Pathway.
Ca2+
F10
F5.
F10a
F5a
Prothrombinase complex.
Ca2+
(Prothrombin.)
F2.
F2a (thrombin)
(Fibrinogen.)
F1.
F1a (fibrin).
F13
F13a
Fibrin stabilizing factor

Hemostasis and Thrombosis

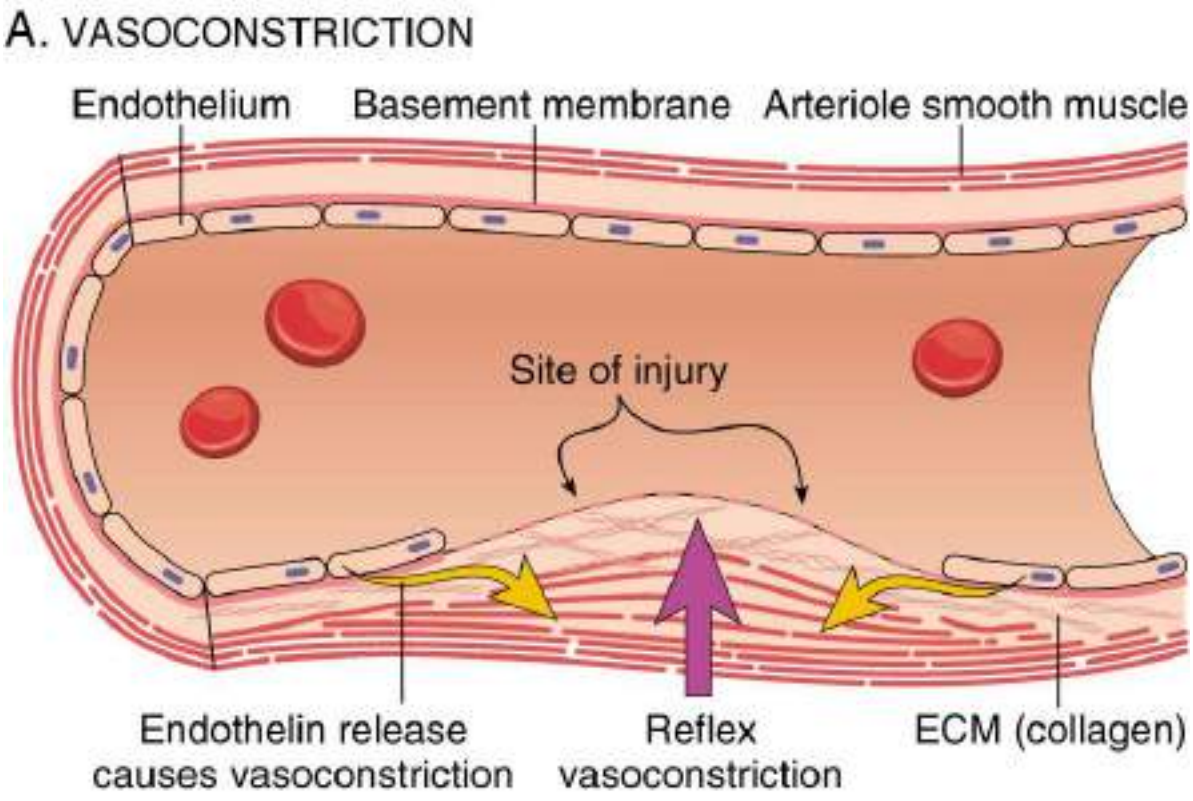
- Hemostasis: physiologic process, maintains blood in fluid condition and clot-free state in normal vessels, and inducing a rapid and localized hemostatic plug at sites of vascular injury.
- It control bleeding at the site of injury , blood loss stop by formation of blood clot that seals the blood vesseles
- Thrombosis: pathologic process, formation of intra-vascular solid mass (thrombus) from the elements of circulating blood. The vessel may be uninjured or with minor injury.

Hemostasis

- Hemostasis depends on the integrity of
  - Blood vessels transient (VC)
  - Platelets Primary hemostasis
  - Coagulation factors Secondary hemostasis

STEPS IN HEMOSTASIS

(1) Transient arteriolar vasoconstriction due to reflex neurogenic mechanism and secretion of endothelin.

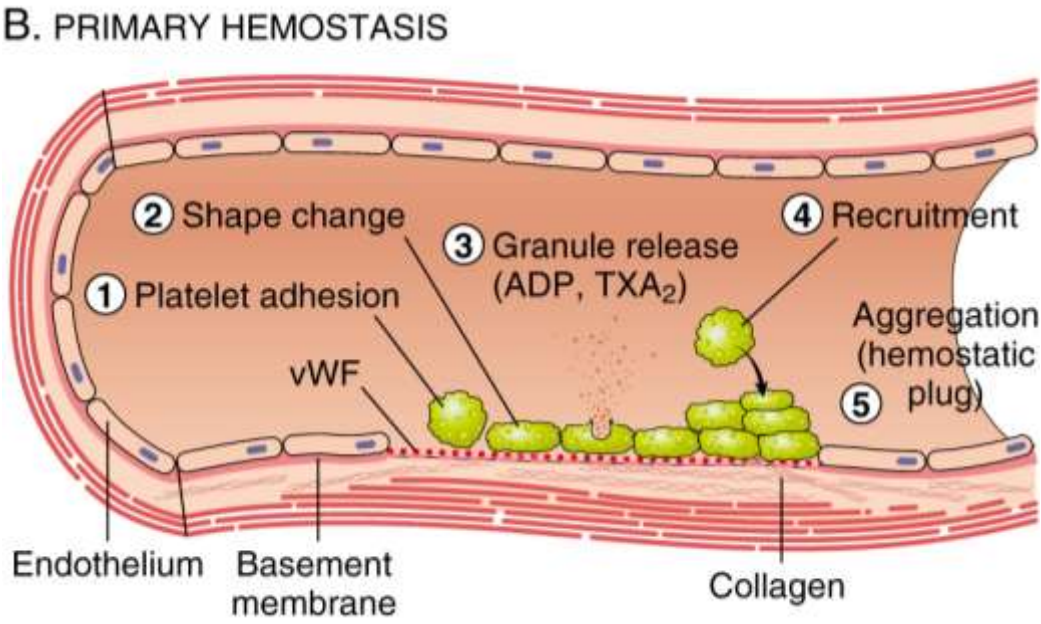


Primary hemostasis

STEPS IN HEMOSTASIS

(2)Formation of primary platelet plug due to adhesion of platelets to collagen and traces of thrombin.

- Adhesion of platelets to the subendothelial ECM via (vWF: von Willebrand factor) then activation of platelets and release of its contents like (TXA_2: thromboxane A_2) and ADP leading to platelets aggregation and formation of hemostatic plug = Weak (primary hemostasis)



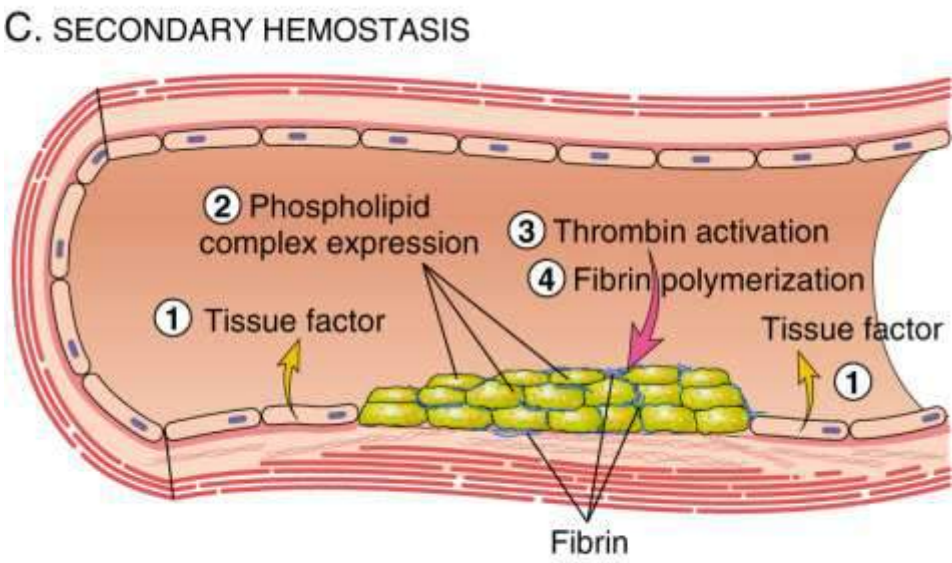
STEPS IN HEMOSTASIS

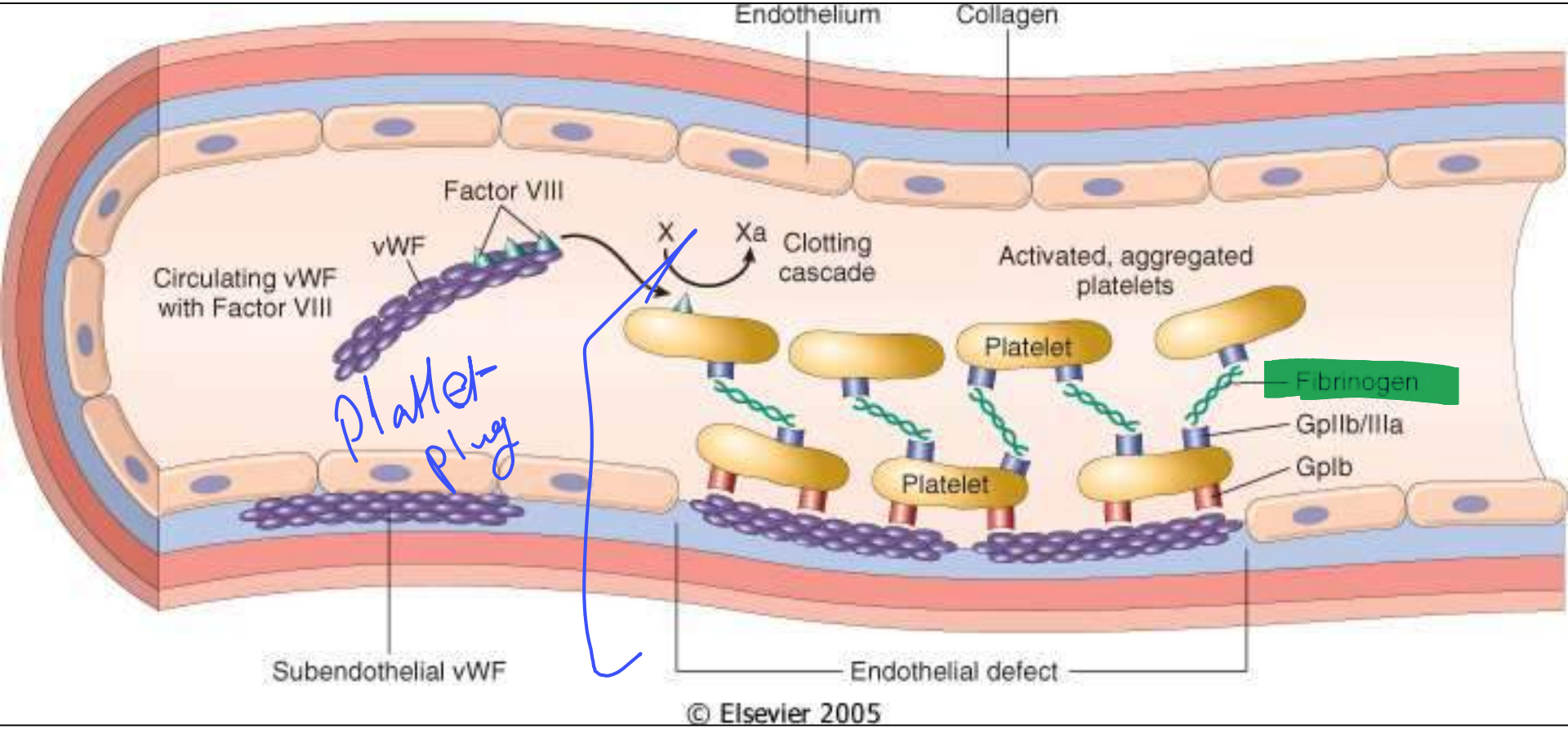
Secondary hemostasis

(3) Conversion into permanent plug supported by fibrin clot, which is formed by activation of the **coagulation cascade**.

- At sites of injury: release of Tissue factor and activation of **extrinsic** coagulation cascade leading to formation of thrombin which converts fibrinogen into insoluble fibrin which binds to the platelet aggregate and stabilize it and this is called **secondary haemostasis.**

F3a F2a F1a




Endothelium
Collagen
Factor VIII
vWF
Circulating vWF
with Factor VIII
X
Xa
Clotting
cascade
Activated, aggregated
platelets
Platelet
Platelet
Fibrinogen
GpIIb/IIIa
GpIb
Platelet-
Plug
Subendothelial vWF
Endothelial defect
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Antithrombotic Functions
Fibrinolytic Effects

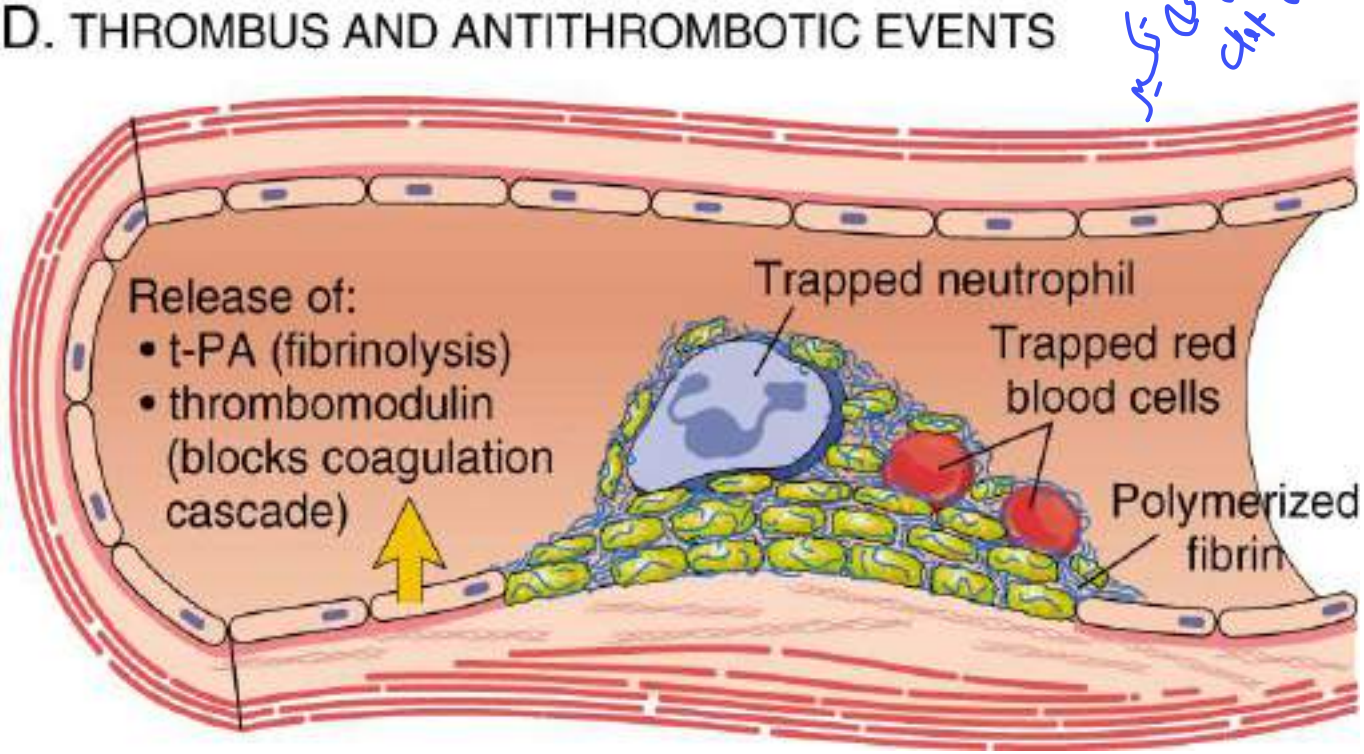
(4) Lysis of fibrin and confinement of clot to the site of injury.

- Fibrinolytic Effect: synthesize tissue-type plasminogen activator (t-PA) that clears fibrin deposits from endothelial surfaces.

TPA

TPA

blasminogen----------> plasmin



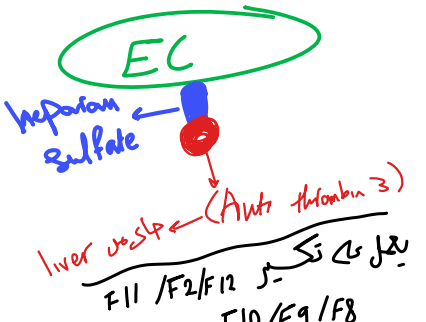
Endothelium

intact is an anti-clotting endothelium

intact. or. injured

Antithrombotic Properties of Normal Endothelium:

1. **Inhibitory Effects on Platelets:**
   - Intact endothelium prevents platelets from engaging the highly thrombogenic subendothelial ECM.
2. Prostacyclin and nitric oxide produced by endothelium are potent vasodilators and inhibitors of platelet aggregation
3. Endothelial cells produce adenosine diphosphatase, which degrades adenosine diphosphate (ADP)



2 Inhibitory Effects on Coagulation Factors:

1 Heparan Sulfate
The heparin-like molecules: Activates **antithrombin**

2
- **Thrombomodulin:** activates **protein C (anticoagulant)**

3 **Tissue factor pathway inhibitor** (TFPI)

3 Fibrinolysis.

- Endothelial cells synthesize tissue-type plasminogen activator, a protease that cleaves plasminogen to plasmin
- Plasmin cleaves fibrin.

Prothrombotic Properties of Injured or Activated Endothelium

- **Activation of Platelets.**

- Endothelial injury brings platelets into contact with the von Willebrand factor (vWF), a large multimeric protein that is synthesized by EC.

- vWF binds tightly to Gp1b, a glycoprotein found on the surface of platelets.

- **Activation of Clotting Factors.**

- Endothelial cells produce tissue factor

- **Antifibrinolytic Effects.**

- Activated endothelial cells secrete plasminogen activator inhibitors (PAIs)

Platelets

lack of nucleus

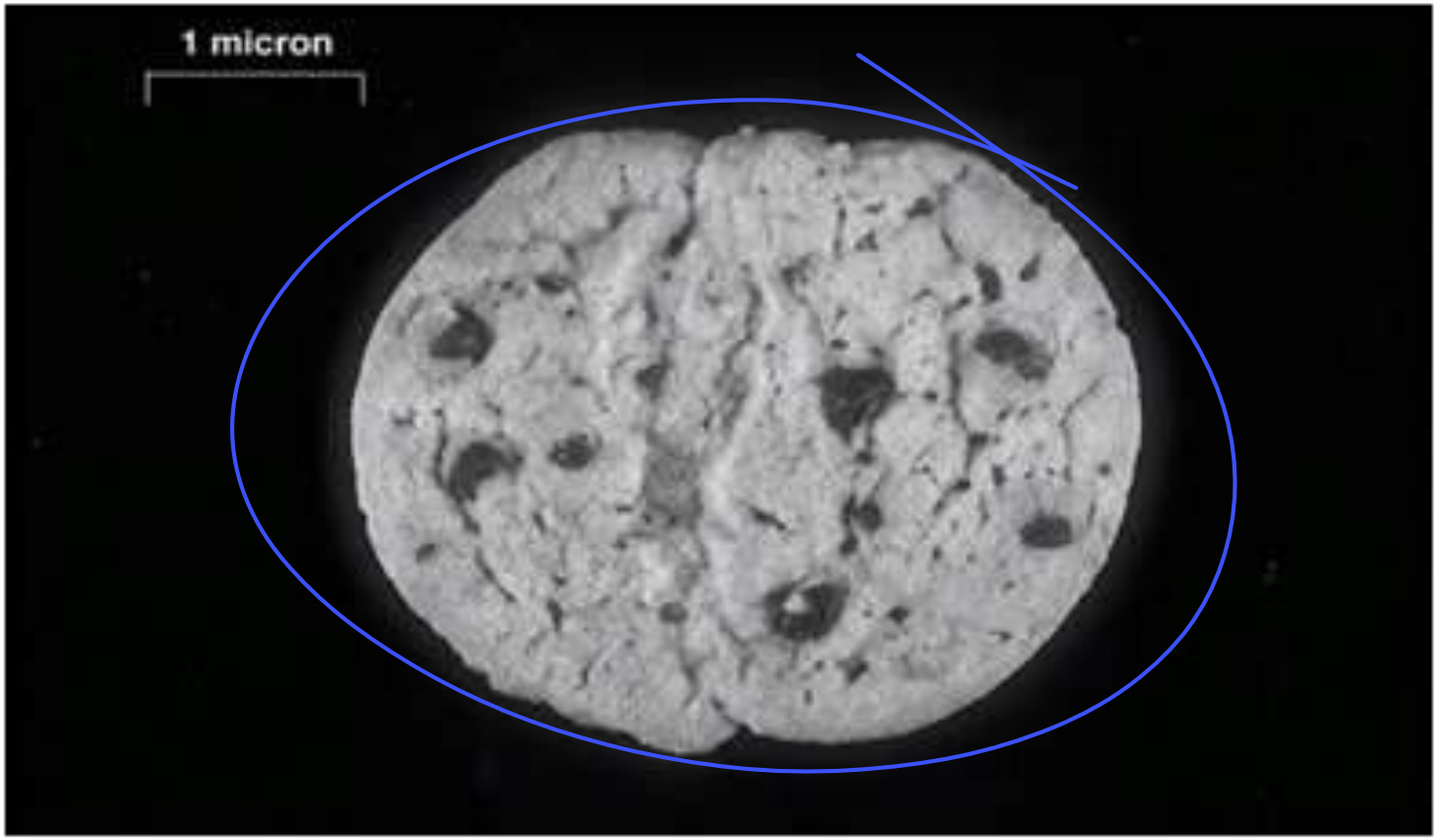
- anucleate cell fragments shed into the bloodstream by marrow megakaryocytes.
- Two types of cytoplasmic granules:

A. α granules

B. Dense bodies (δ granules): contain adenine nucleotides (ADP and ATP), ionized calcium, histamine, serotonin,and epinephrine

& TXA2 + Platlet derived factor

Here is an actual electron micrograph of a platelet. Note that this platelet bears a striking resemblance to a chocolate chip cookie. The chocolate chips are the alpha and dense granules that contain a variety of mediators such as ADP.



After vascular injury:

1- Platelet **Adhesion**

- Depends on vWF and platelet glycoprotein **Gp1b**.

2- Platelet **Activation**

- Irreversible shape change and secretion of both granule types.
- Calcium and ADP released
- **Calcium is required by several coagulation factors**
- Activated platelets also synthesize TxA2

After vascular injury:

3- Platelet **Aggregation** → new platelets التعاق ال

- Stimulated by TxA2.
- Promoted by bridging interactions between **fibrinogen and GpIIb/IIIa** receptors on adjacent platelets .
- Rare inherited deficiency of GpIIb/IIIa (Glanzmann thrombasthenia)

platlet agregation يعتمد الى

secondary homesteases occurs under the control of clotting factors

coagulation cascade

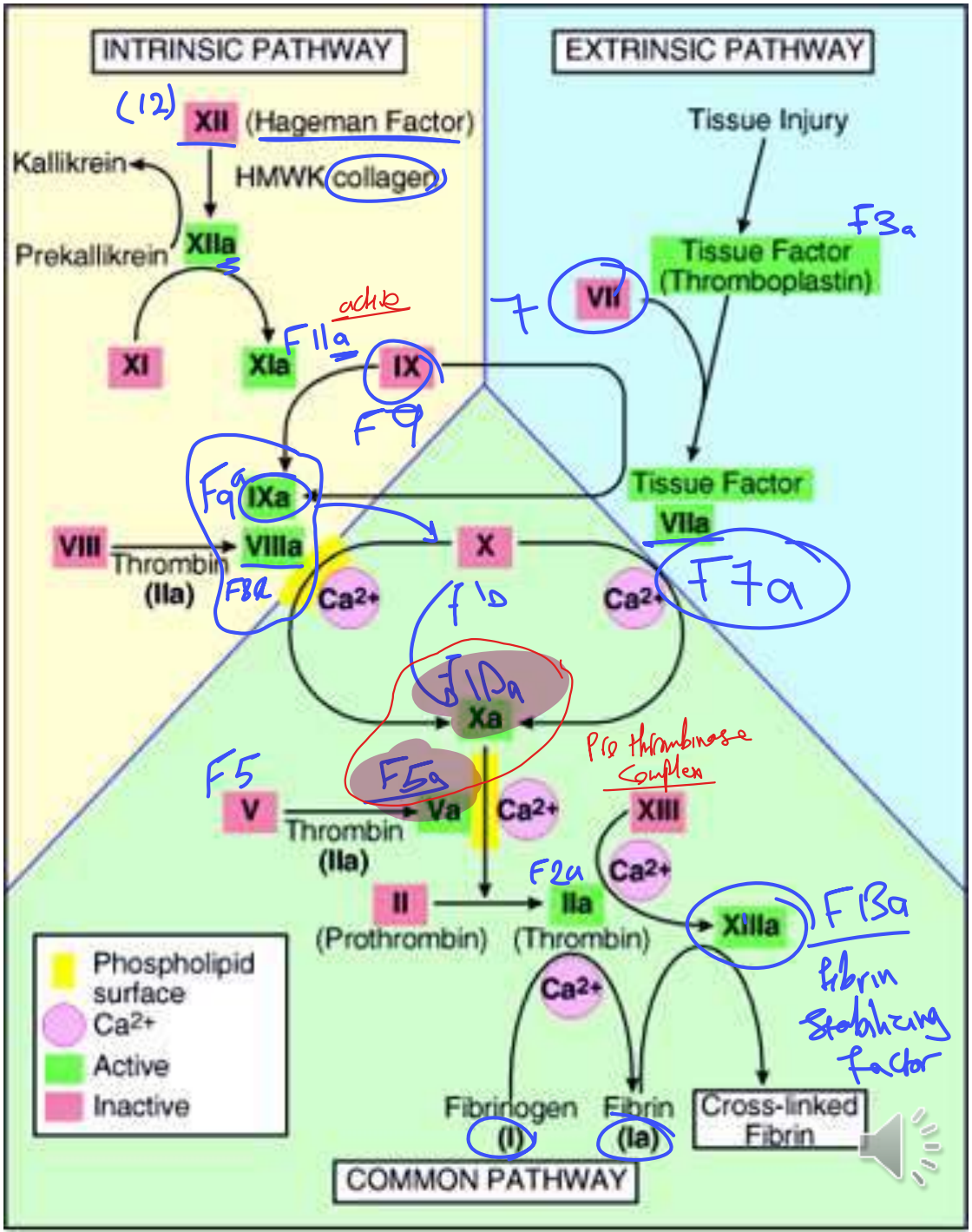
- Coagulation components typically are assembled on a phospholipid surface (provided by endothelial cells or platelets)
- Coagulation components are held together by interactions that depend on **calcium ions**
- The ability of coagulation factors **II, VII, IX, and X** to bind to calcium requires that additional γ-carboxyl groups be enzymatically appended to certain glutamic acid residues on these proteins.

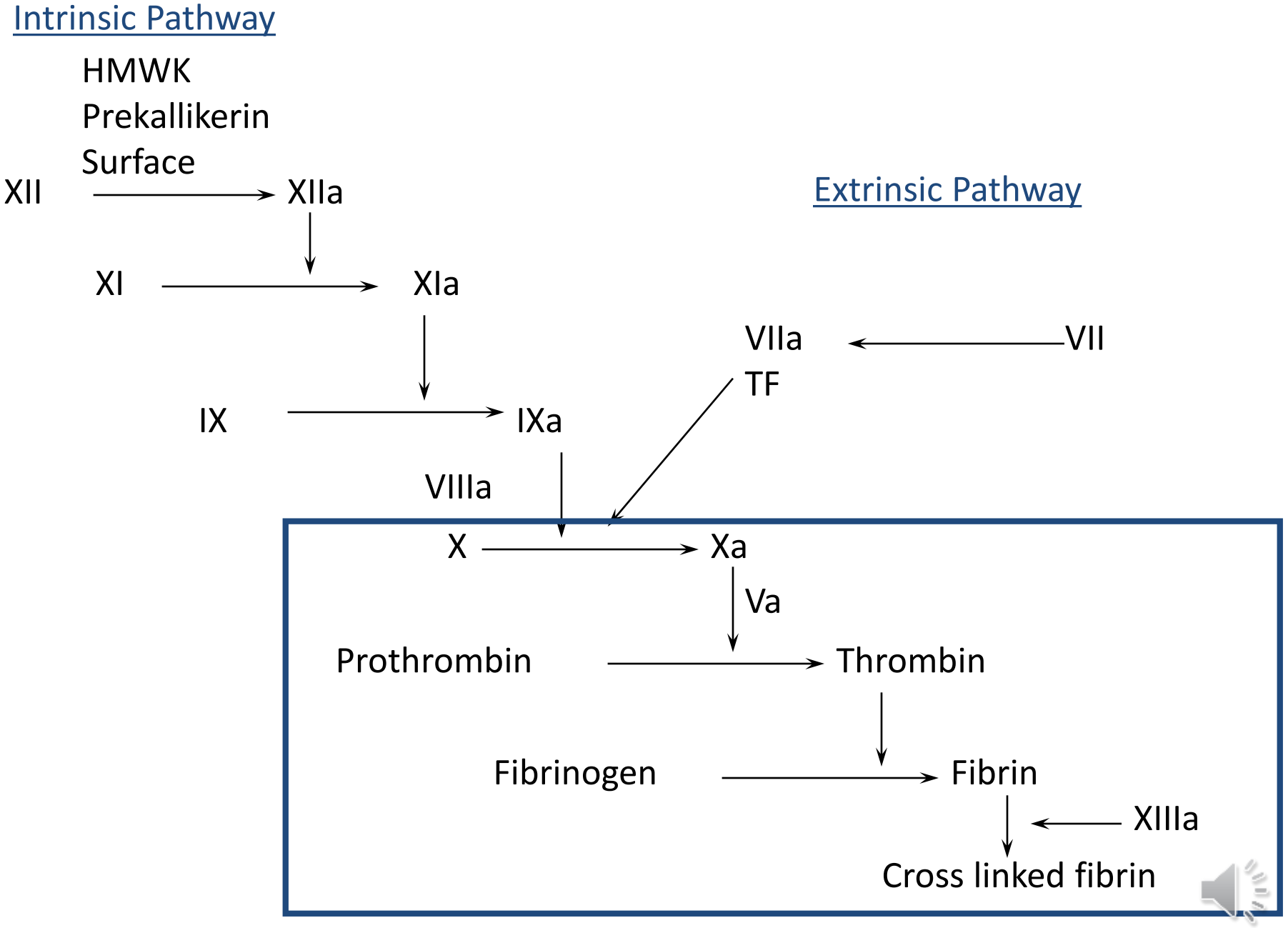
- This reaction requires vitamin K as a cofactor

- Blood coagulation divided into **extrinsic** and **intrinsic** pathways, converging at the **activation of factor X**.
- Several interconnections between the two pathways exist.
- The **extrinsic** pathway is the most physiologically relevant pathway for coagulation occurring after vascular damage; it is activated by **tissue factor**.

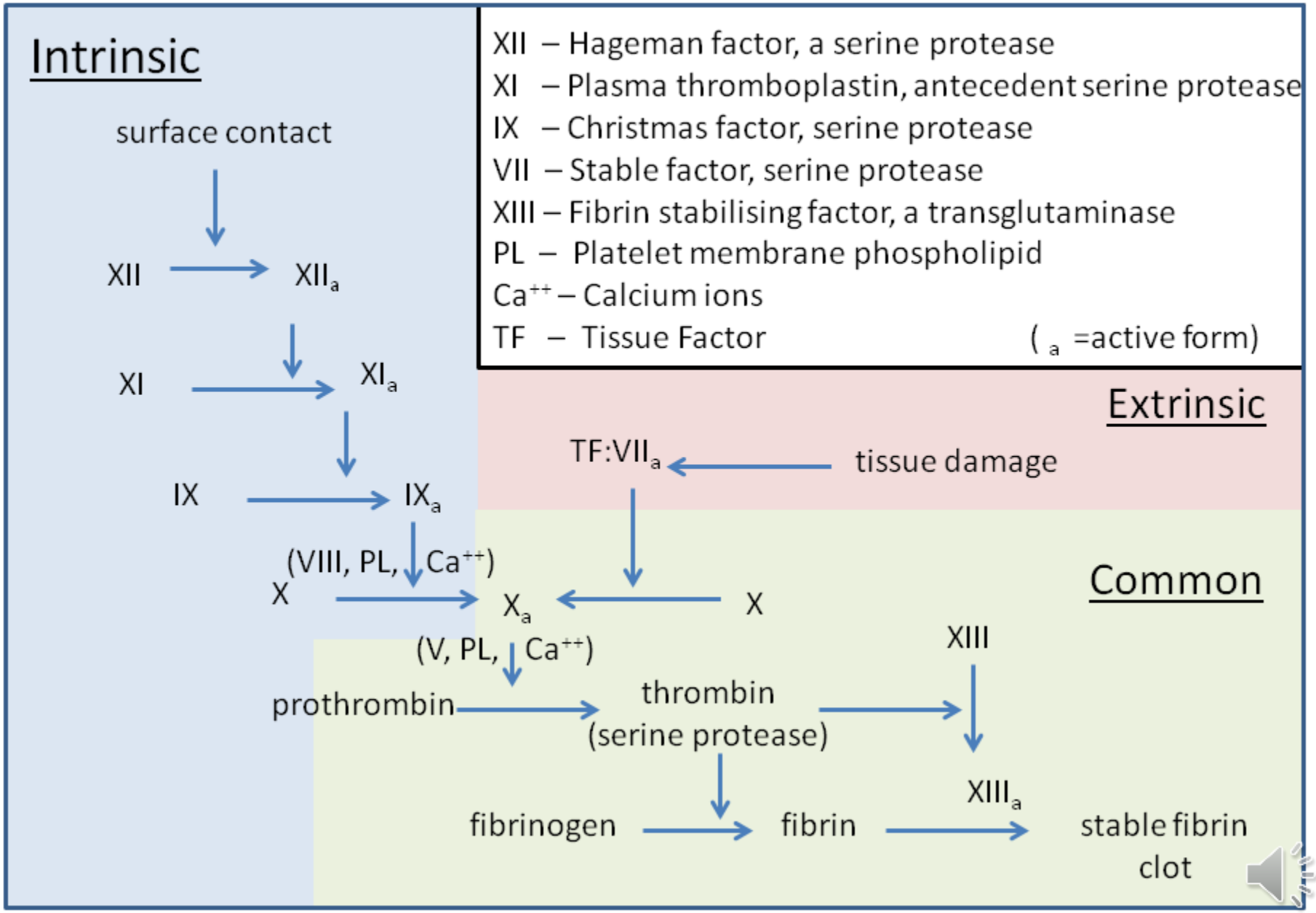
The coagulation cascade

- Factors in red boxes represent inactive molecules.
- Activated factors are indicated with a lower case "a" and a green box.
- HMWK (high molecular weight kininogen).




Intrinsic Pathway
HMWK
Prekallikerin
Surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
Extrinsic Pathway
VIIa
VII
TF
X
Xa
Va
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIIIa
Cross linked fibrin

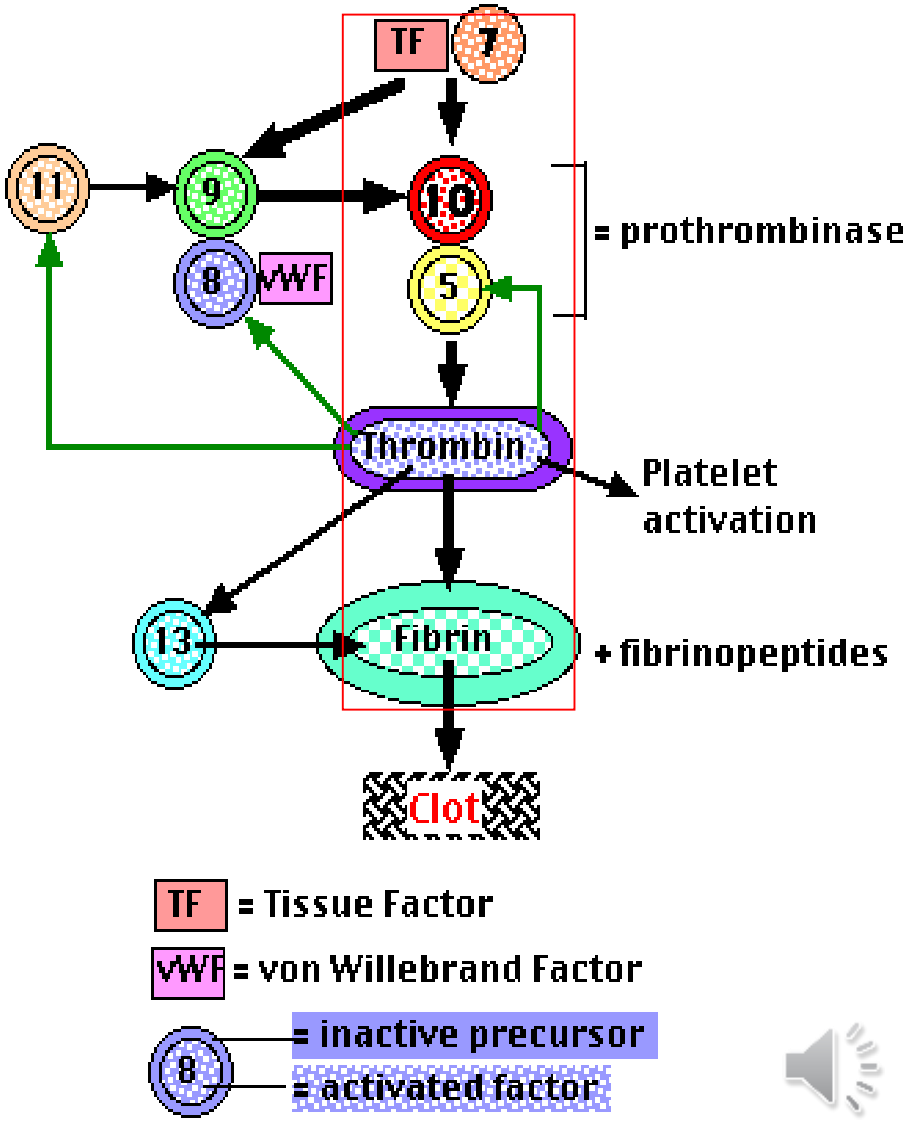
The three pathways that makeup the classical blood coagulation pathway



Coagulation cascade

1. Damaged cells (extrinsic pathway) display a surface protein (tissue factor: TF) that binds to activated Factor 7 (TF-7) to cleave: Factor 10

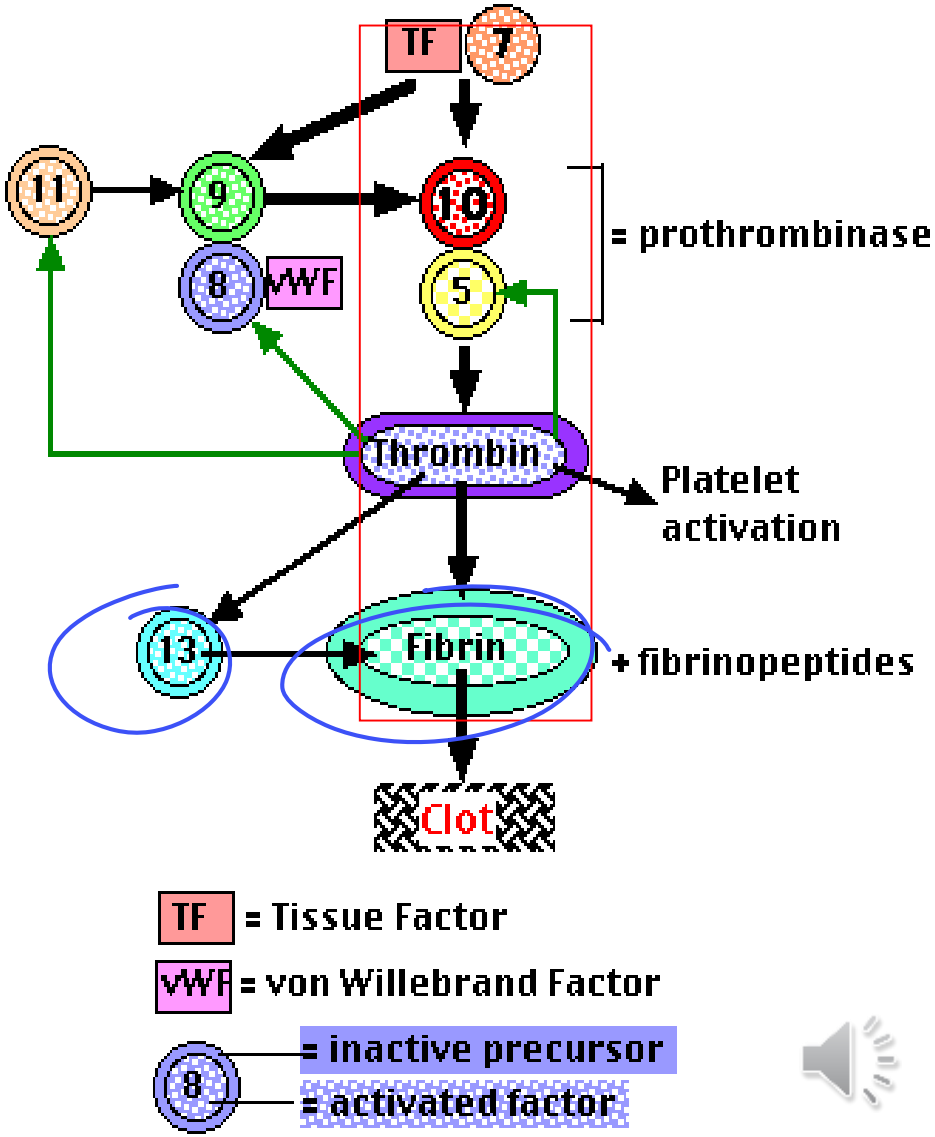
2. Factor 10 binds and activates Factor 5 (prothrombinase) converting prothrombin (also known as Factor II) to thrombin



Coagulation cascade

3. Thrombin proteolytically cleave fibrinogen (Factor I) to fibrin.

4. Factor 13 forms covalent bonds between the soluble fibrin molecules converting them into an insoluble meshwork — the clot.

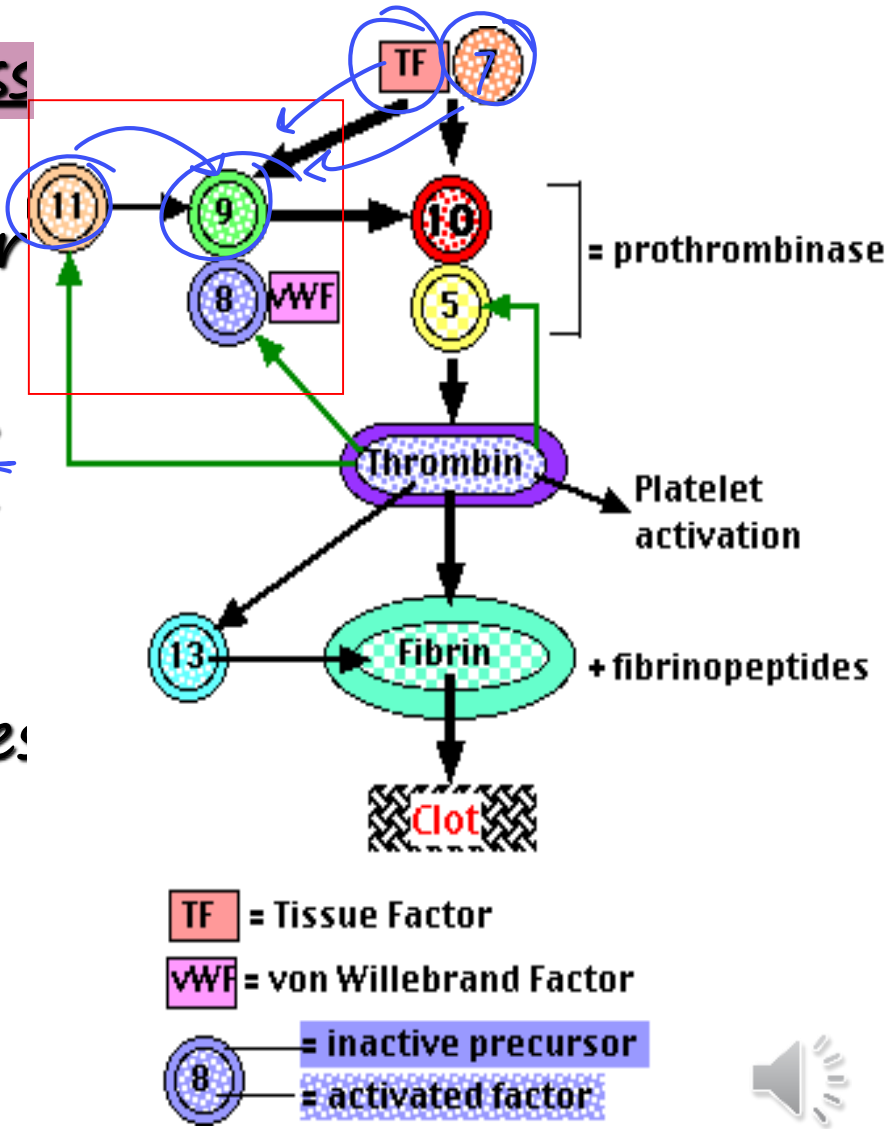


Coagulation cascade

Amplifying the Clotting Process

- The TF-7 complex & factor 11 activates Factor 9.
- Factor 9 binds to factor 8, a protein that circulates in the blood stabilized by another protein (vWF).
- Complex 9-8-vWF activates more factors: 5,10

(VWF) ← Factor(8) یاد بده تقویه



Coagulation factors and related substances

Number and/or name	Function
I (fibrinogen)	Forms clot (fibrin)
II (prothrombin)	Its active form (IIa) activates I, V, VIII, XI, XIII, protein C, platelets
III (Tissue factor or thromboplastin	Co-factor of VIIa
IV (Calcium)	Required for coagulation factors to bind to phospholipid
V (proaccelerin, labile factor)	Co-factor of X with which it forms the prothrombinase complex
VI	Unassigned – old name of Factor Va
VII (stable factor)	Activates IX, X
VIII (antihemophilic factor)	Co-factor of IX with which it forms the tenase complex
IX (Christmas factor)	Activates X: forms tenase complex with factor VIII
X (Stuart-Prower factor)	Activates II: forms prothrombinase complex with factor V
XI (plasma thromboplastin antecedent)	Activates IX
XII (Hageman factor)	Activates factor XI and prekallikrein
XIII (fibrin-stabilizing factor)	Crosslinks fibrin
von Willebrand factor	Binds to VIII, mediates platelet adhesion

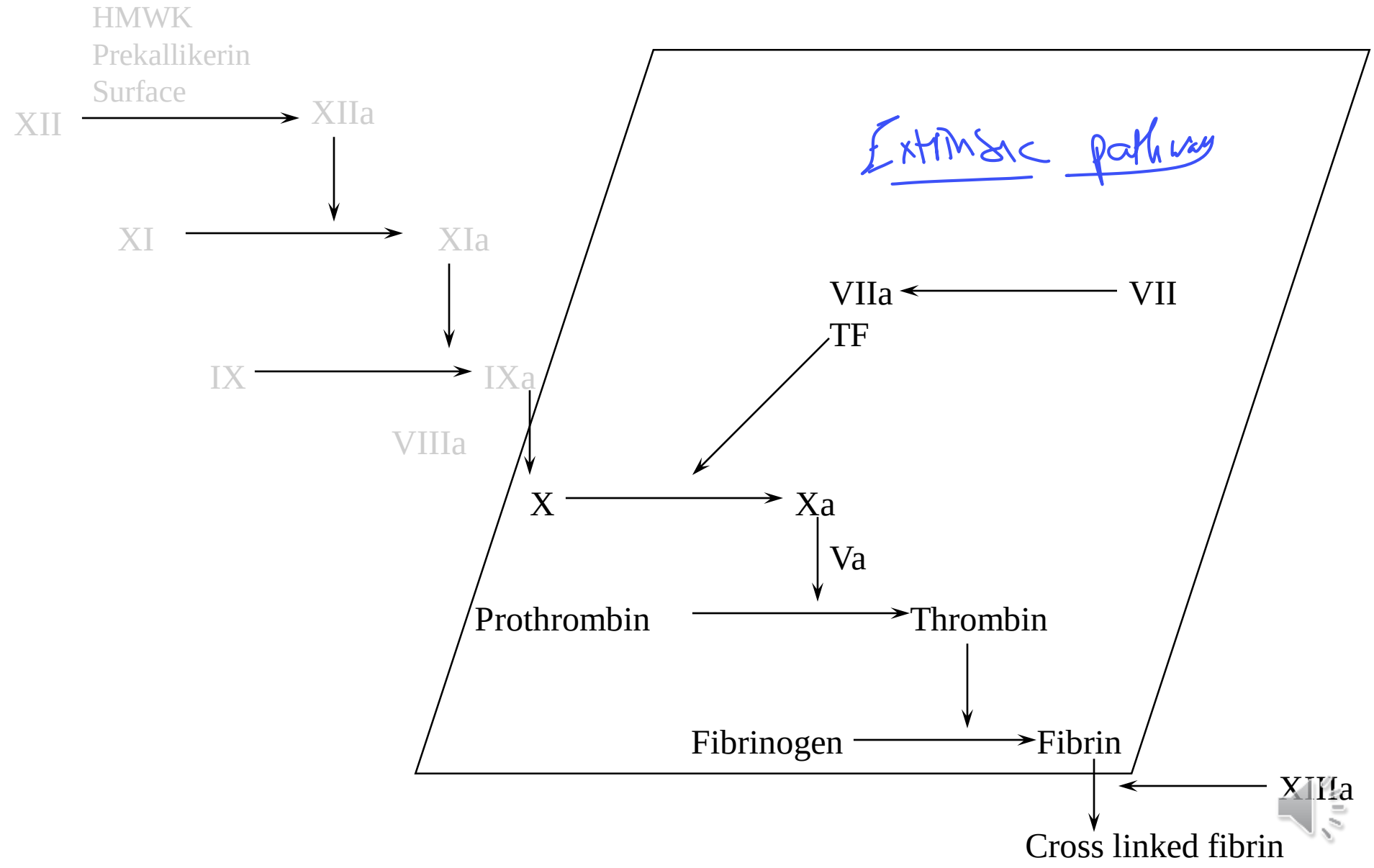
Coagulation factors and related substances

prekallikrein	Activates XII and prekallikrein; cleaves HMWK
high molecular weight kininogen (HMWK)	Supports reciprocal activation of XII, XI, and prekallikrein
fibronectin	Mediates cell adhesion
antithrombin III	Inhibits IIa, Xa, and other proteases;
heparin cofactor II	Inhibits IIa, cofactor for heparin and dermatan sulfate ("minor antithrombin")
protein C	Inactivates Va and VIIIa
protein S	Cofactor for activated protein C (APC, inactive when bound to C4b-binding protein)
protein Z	Mediates thrombin adhesion to phospholipids and stimulates degradation of factor X by ZPI
Protein Z-related protease inhibitor (ZPI)	Degrades factors X (in presence of protein Z) and XI (independently)
plasminogen	Converts to plasmin, lyses fibrin and other proteins
alpha 2-antiplasmin	Inhibits plasmin
tissue plasminogen activator (tPA)	Activates plasminogen
urokinase	Activates plasminogen
plasminogen activator inhibitor-1 (PAI1)	Inactivates tPA & urokinase (endothelial PAI)
plasminogen activator inhibitor-2	Inactivates tPA & urokinase (placental PAI)

Clinical labs assessment

- **Prothrombin time (PT):**
  - Screens for the activity of the proteins in the **extrinsic** pathway (factors **VII**, X, II, V, and fibrinogen).
  - The PT is performed by adding phospholipids and tissue factor to a patient's citrated plasma (sodium citrate chelates calcium and prevents spontaneous clotting), followed by calcium, and the time to fibrin clot formation (usually 11 to 13 seconds) is recorded.

Prothrombin Time(PT)



- **Partial thromboplastin time (PTT):**

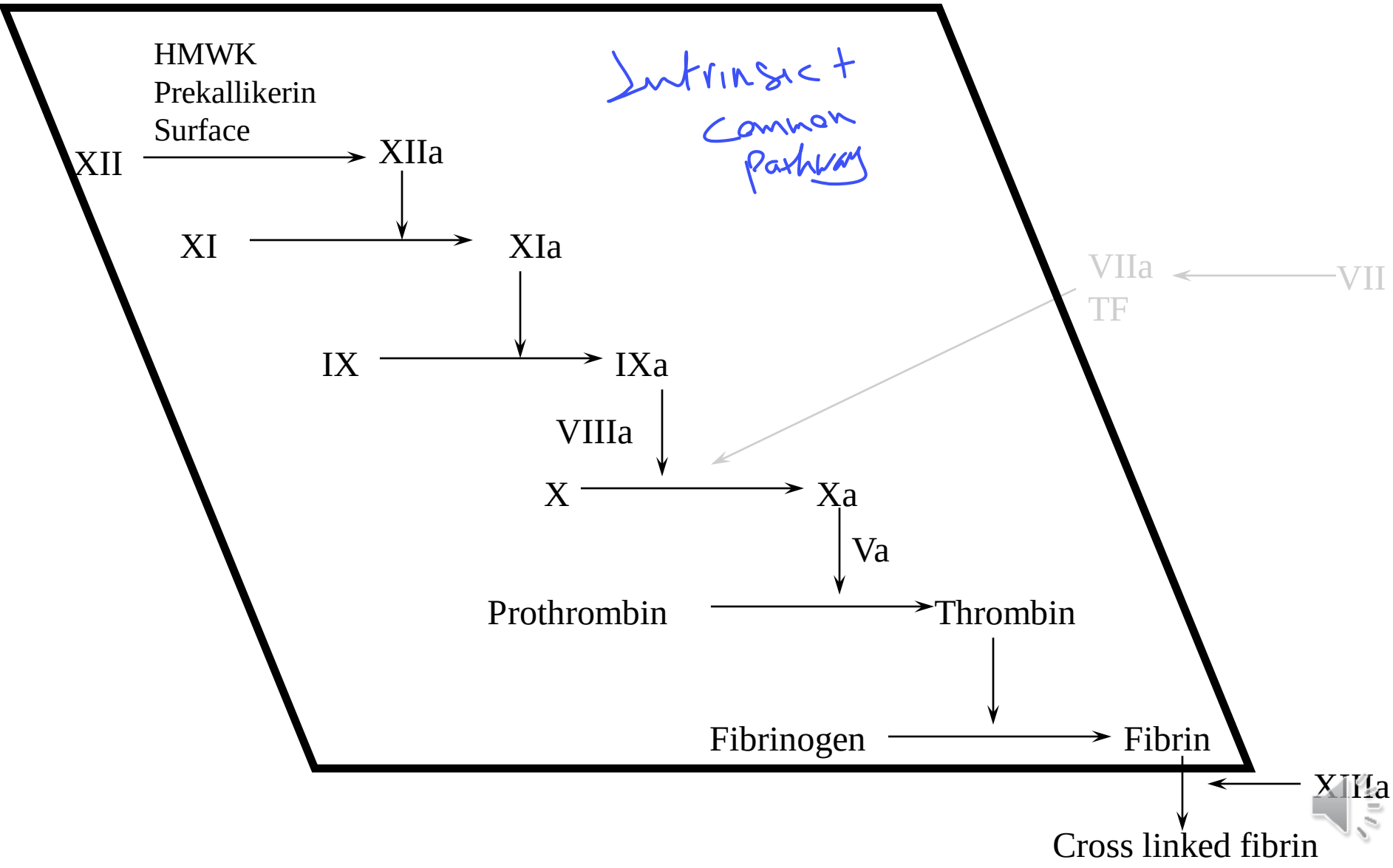
- Screens for the activity of the proteins in the **intrinsic** pathway (factors **XII, XI, IX, VIII**, X, V, II, and fibrinogen).

Common pathway

12 11 9 8 10 5

  - The PTT is performed by adding a negatively charged activator of factor XII and phospholipids to a patient's citrated plasma, followed by calcium, and recording the time required for clot formation (usually 28 to 35 seconds).

Partial Thromboplastin Time

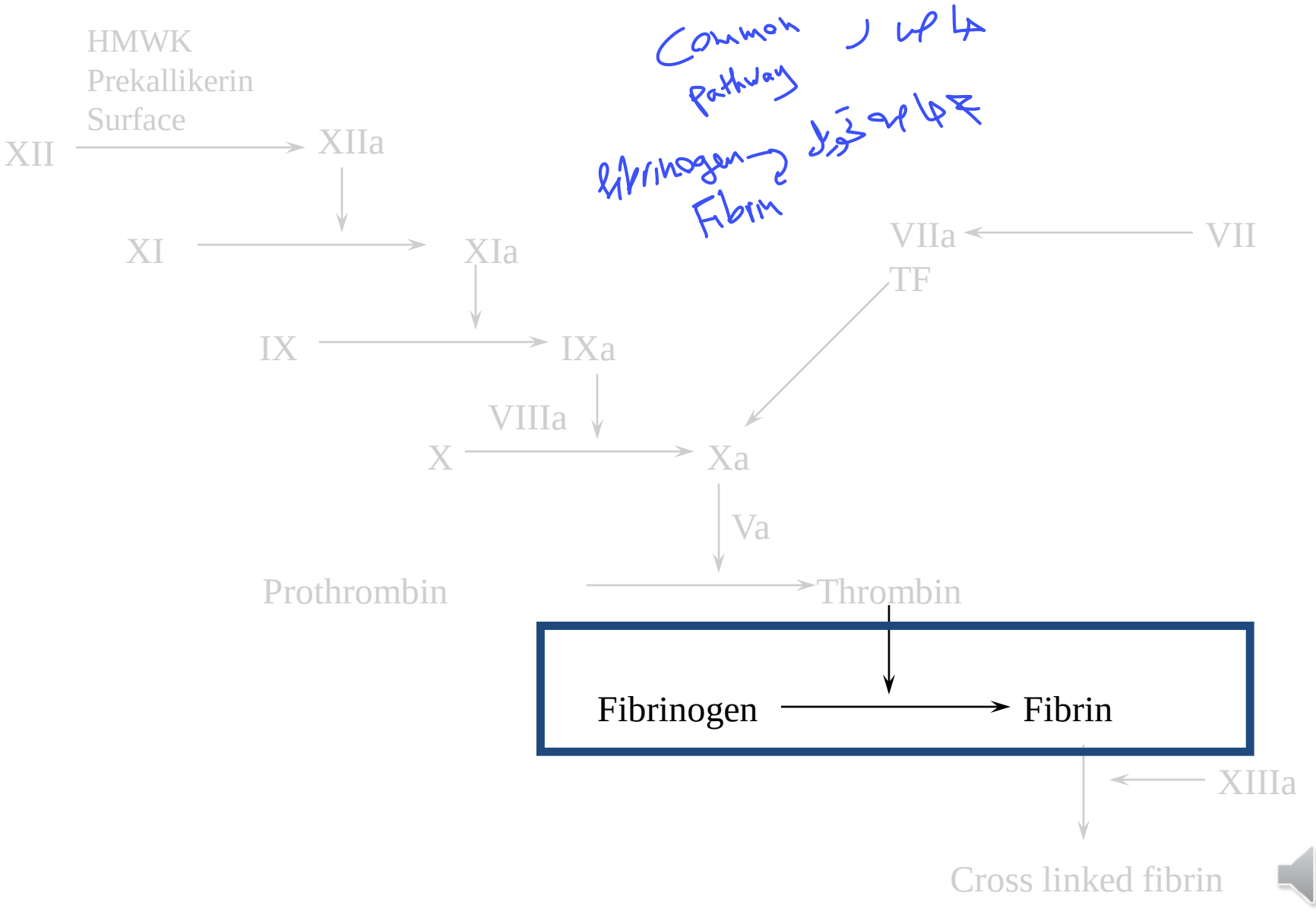


Common pathway يقيس مدى عمل

- **Thrombin Time:**

- screen for reduction of fibrinogen concentration and presence of fibrin split products.
- Thrombin is added to plasma. Time needed to clot is measured as TT.

Thrombin Time



Regulation of clotting

1- **Antithrombins** (e.g., antithrombin III) :

- Inhibit the activity of thrombin and factors **IXa, Xa, XIa, and XIIa.**
- Activated by binding to **heparin-like molecules**

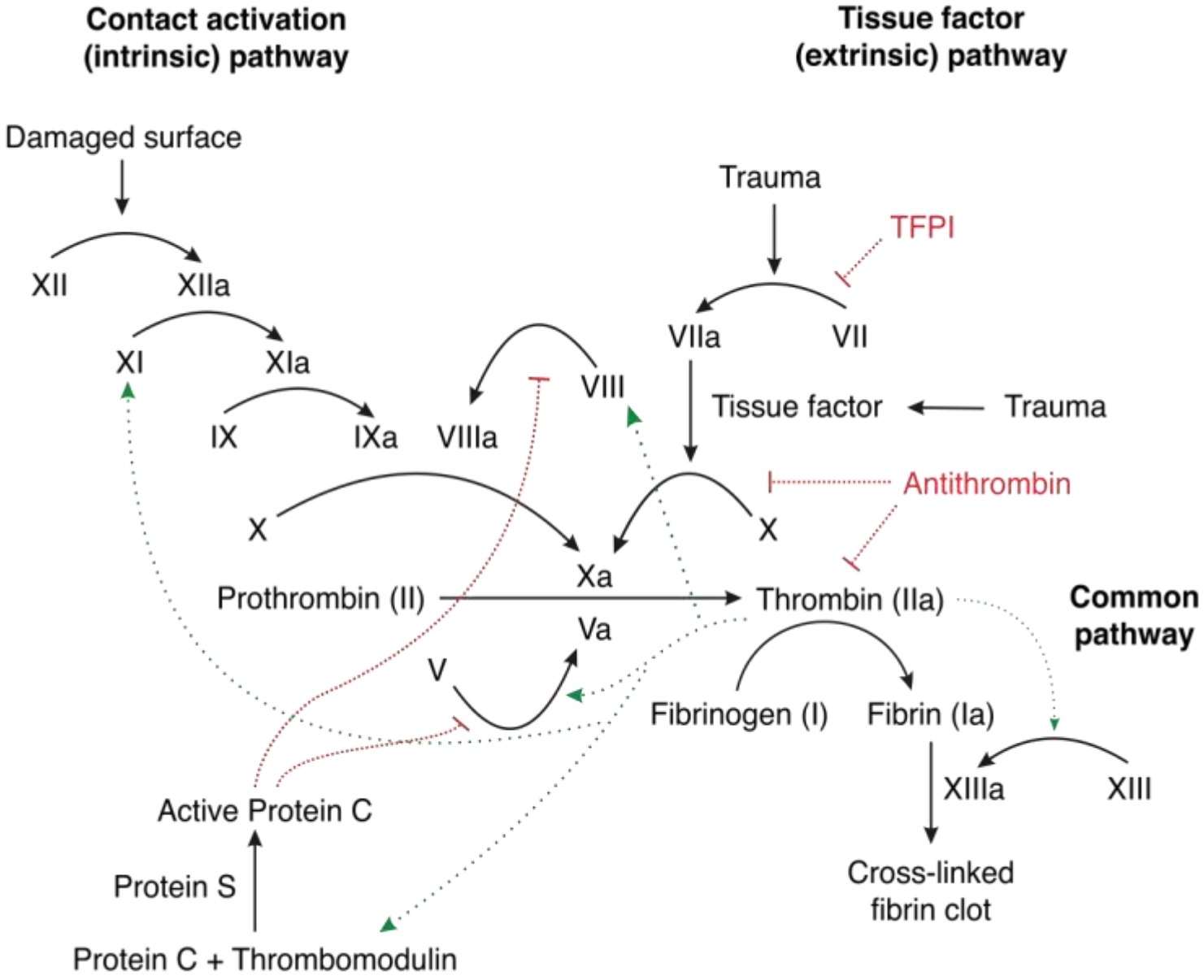
2- Protein C and protein S:

- Two vitamin K–dependent proteins that act in a complex to proteolytically **inactivate cofactors Va and VIIIa.**
- Protein C **activated by thrombomodulin**
- protein S is a cofactor for protein C activity

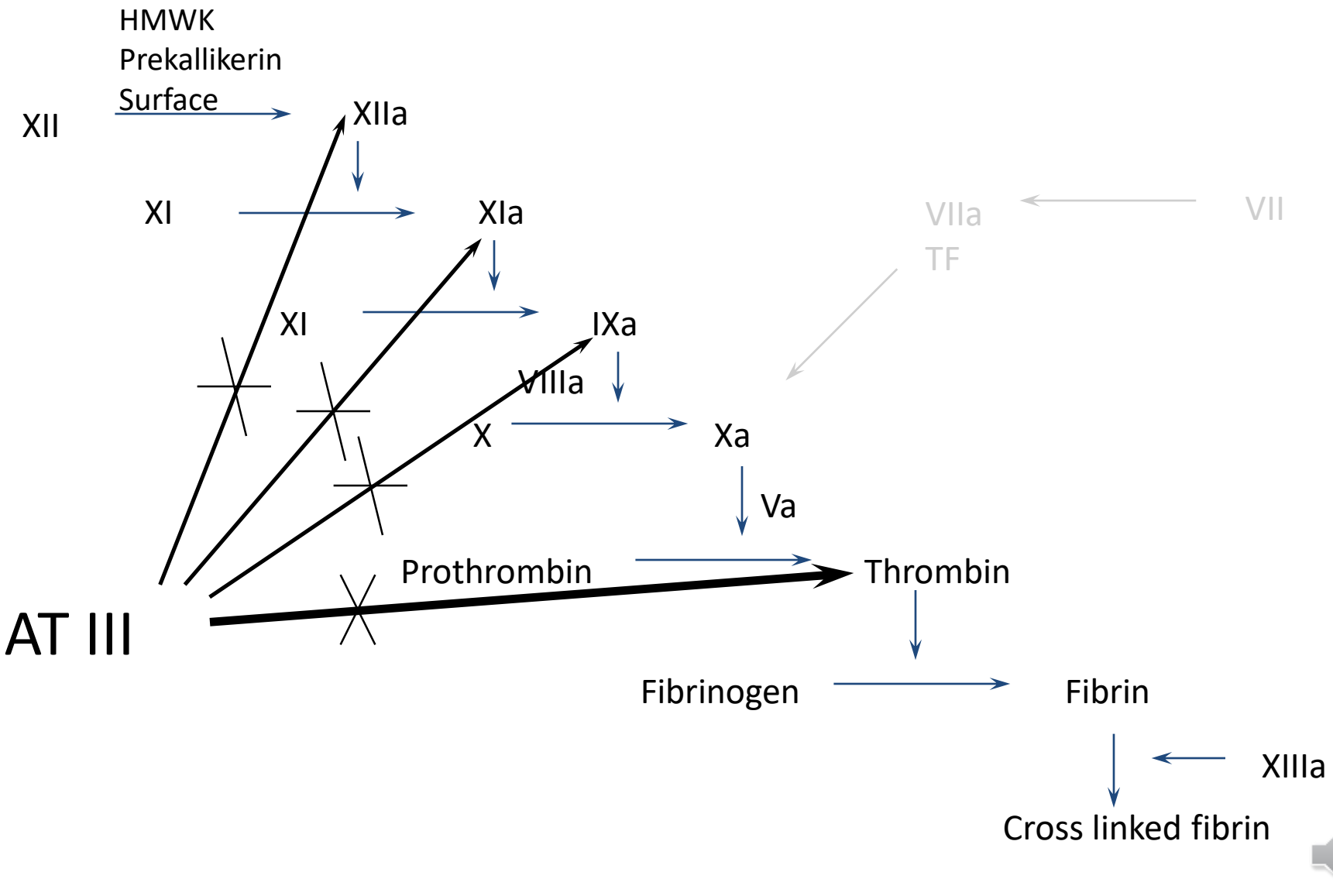
3-Tissue factor pathway inhibitor (TFPI):

- **Inactivates factor Xa and tissue factor–factor VIIa complexes**

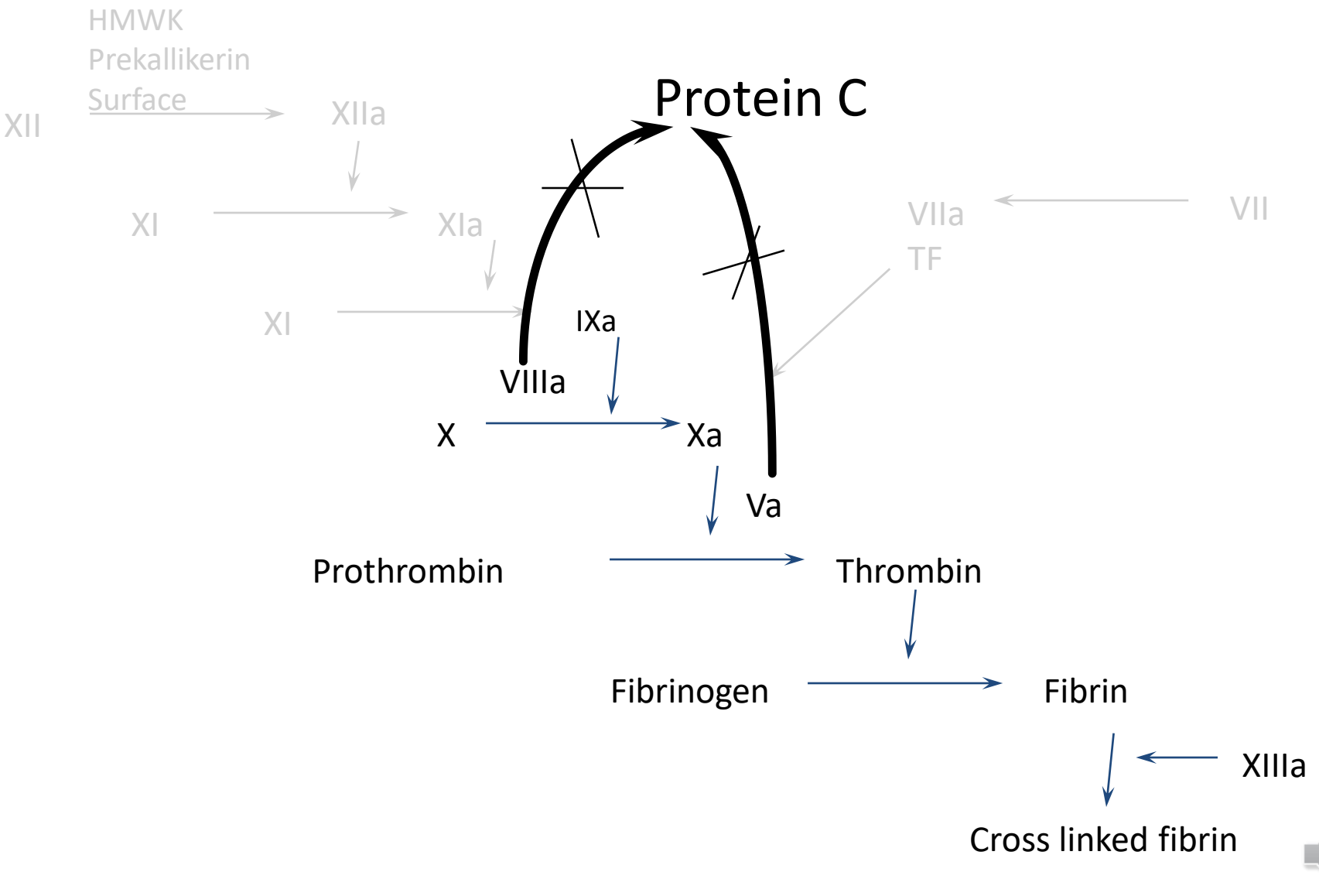
4- Plasmin


Contact activation
(intrinsic) pathway
Tissue factor
(extrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VIII
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
X
Xa
Prothrombin (II)
Thrombin (IIa)
Common
pathway
Va
V
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked
fibrin clot
Active Protein C
Protein S
Protein C + Thrombomodulin

Antithrombin III



Protein C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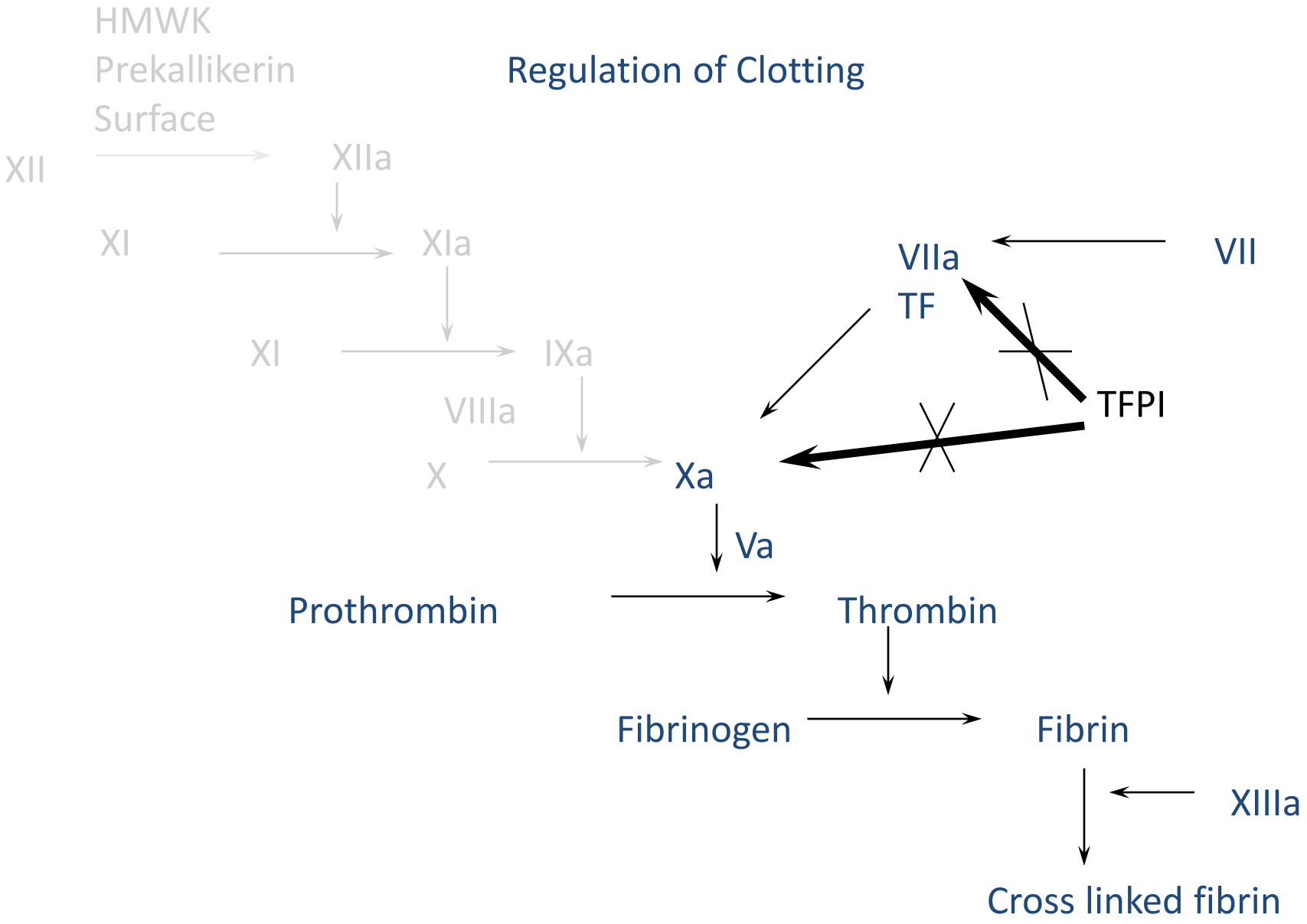
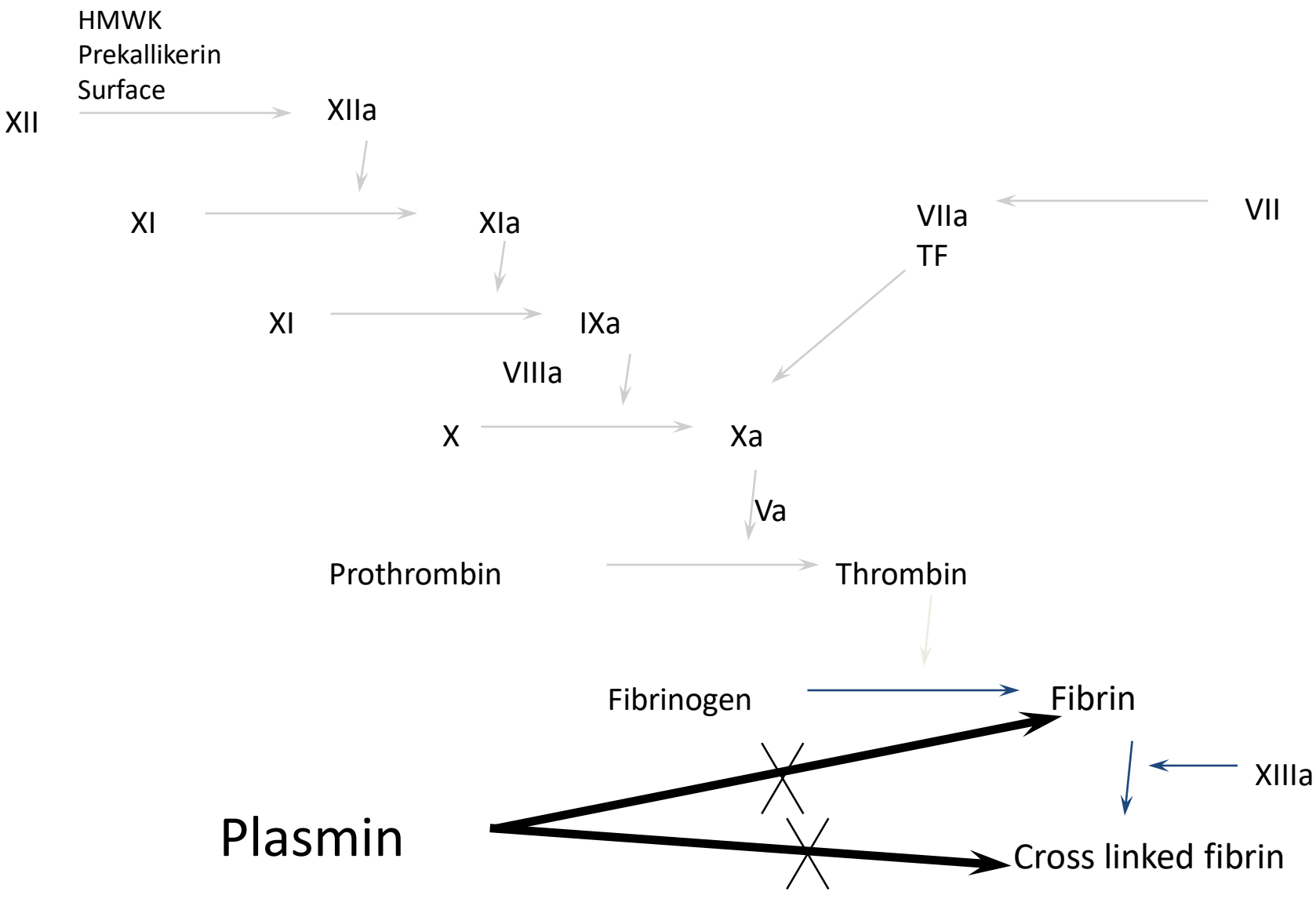
Regulation of Clotting



Plasmin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XIIIa
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Cross linked fibrin

Regulation of Clotting