Pathology

Subject :

Lec no :18

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وقل رب زدني علماً

Hemodynamics lecture 3 +4

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2023
Audio 3

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.

Non injured vessels

- 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.

It causes complete or partial closure of blood vessel so it will lead to ischemia to tissue or organ that supplied by this vessel

Hemostasis

- Hemostasis depends on the integrity of
  - Blood vessels
  - Platelets
  - Coagulation factors

بكونوا موجودين في ال intravascular compartment في ال inactive form و لما يصير اي vascular injury رح تصير active

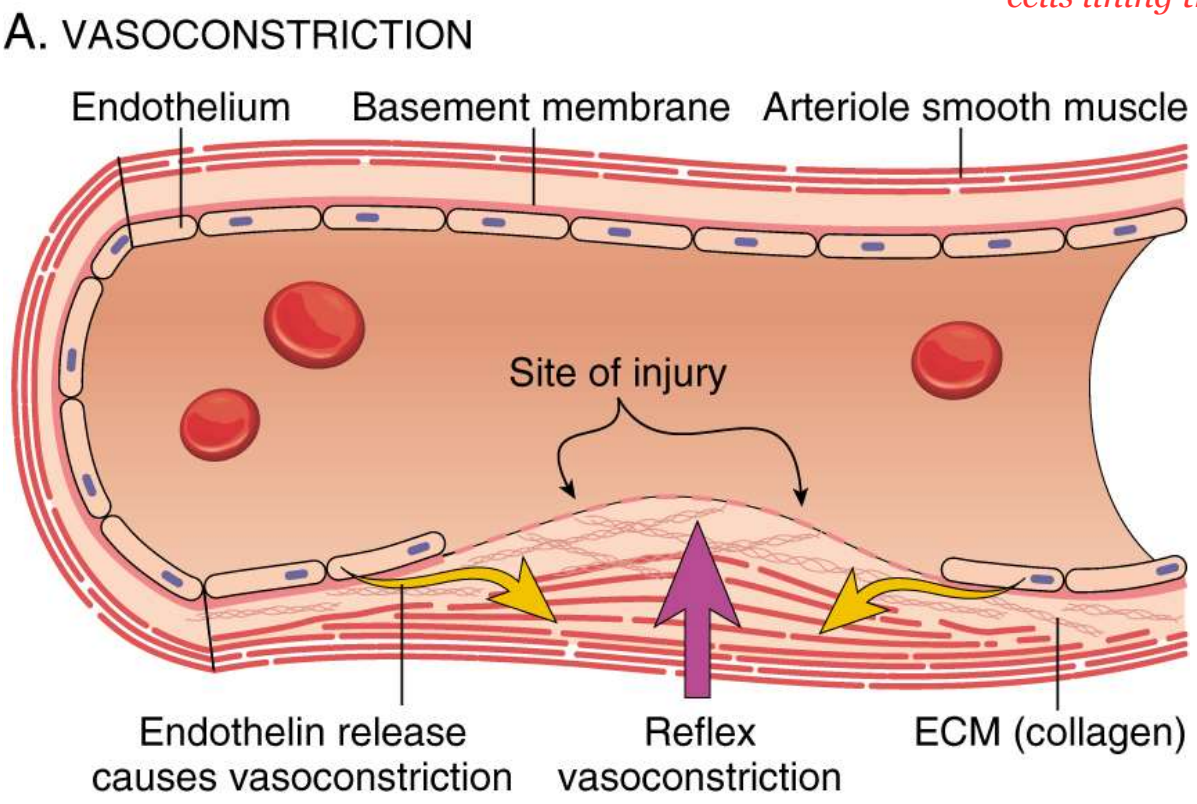
STEPS IN HEMOSTASIS

. *Rapid and Temporary*

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

Nerve fibers in the vicinity of the injury are activated, leading to a reflexive response. This neural activation prompts the release of neurotransmitters that contribute to the constriction of the blood vessels.

produced by the endothelial cells lining the blood vessels



لما يصير عنا vascular injury رح يصير عنا
damage the wall in blood vessels

و بالتالي Including Blood vessel contents
Platelets
رح تصير مواجهة للكولاجين (بعد ال injury رح يصير مكشوف)
و بمجرد وصول ال Platelets للكولاجين رح يصيرلها
activation
و تعمل release لل serotonin

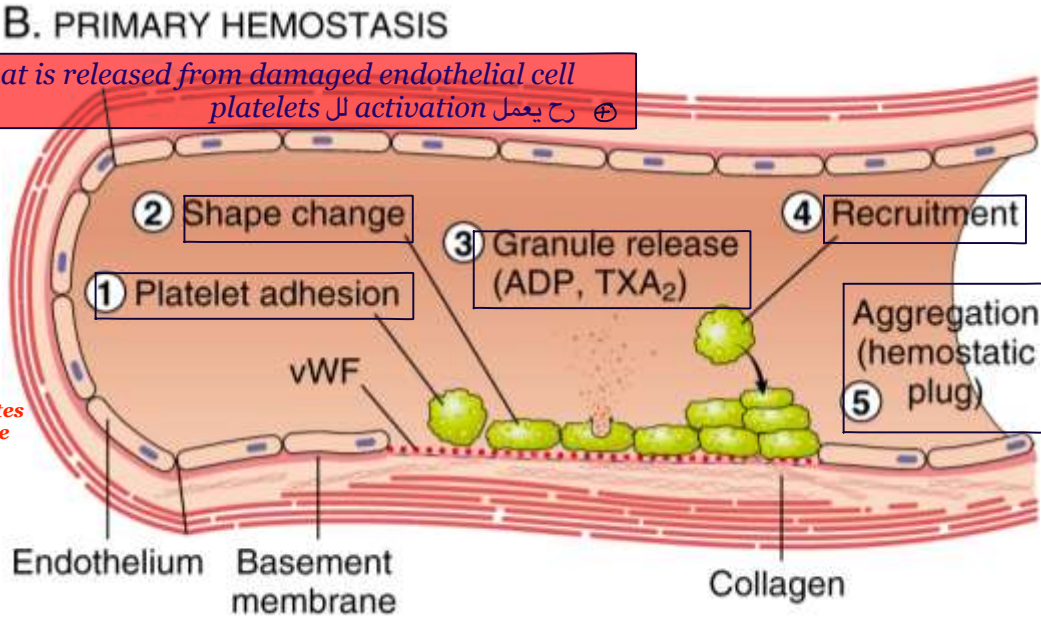
It contributes to vasoconstriction, which helps in reducing blood vessel diameter and minimizing blood loss at the site of injury. Additionally, serotonin plays a role in amplifying platelet aggregation, aiding in the

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 (تجمع) and formation of hemostatic plug (primary hemostasis)

attracts and activates more platelets to the site of injury



1. Adhesion to Collagen and Traces of Thrombin:
   - Platelets adhere to exposed collagen at the site of vascular injury.
   - Traces of thrombin contribute to platelet activation and adhesion.

2. Adhesion via von Willebrand Factor (vWF):
   - von Willebrand factor (vWF) acts as a bridge, facilitating platelet adhesion to the subendothelial extracellular matrix.

3. Activation of Platelets:
   - Adhered platelets undergo activation, leading to changes in shape.

4. Release of Platelet Contents:
   - Platelets release substances like thromboxane A2 (TXA2) and adenosine diphosphate (ADP).

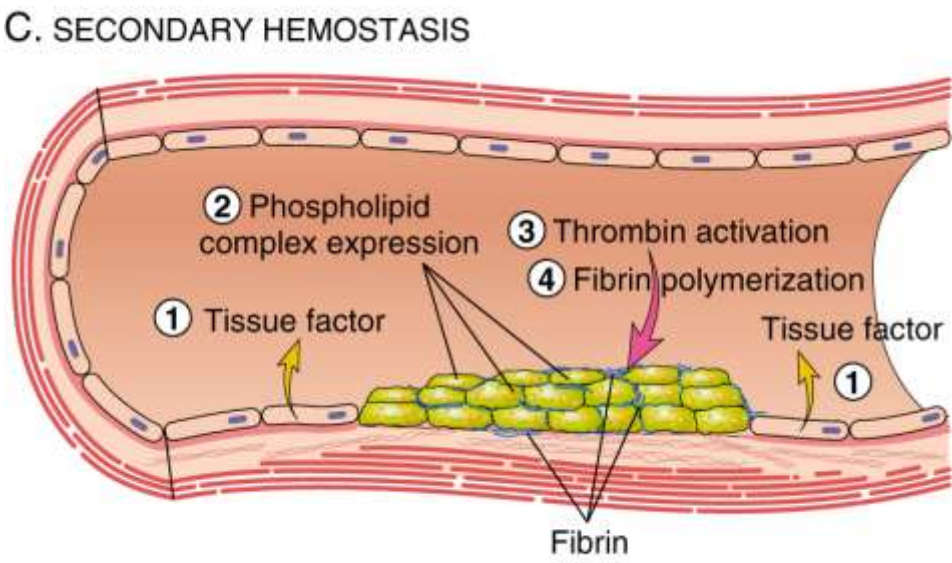
5. Platelet Aggregation:
   - Activated platelets aggregate, sticking together at the site of injury.

6. Formation of Hemostatic Plug (Primary Hemostasis):
   - The aggregated platelets form the primary hemostatic plug, a temporary seal preventing further blood loss.

STEPS IN 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.**



a. Coagulation Cascade Activation:

- **The third step involves the activation of the coagulation cascade, which is leading to the formation of a fibrin clot.**
- **Coagulation is initiated by the release of tissue factor at the site of injury.**

b. Tissue Factor and Extrinsic Coagulation Cascade:

- **Tissue factor is released at the site of injury, triggering the extrinsic coagulation cascade.**
- **The extrinsic pathway involves a series of clotting factors leading to the activation of factor X.**

c. Formation of Thrombin:

- **Activated factor X, along with other factors, leads to the formation of thrombin.**
- **Thrombin is a key enzyme that converts fibrinogen, a soluble plasma protein, into insoluble fibrin strands.**

d. Fibrinogen to Fibrin Conversion:

- **Thrombin acts on fibrinogen, cleaving it into fibrin monomers.**
- **These fibrin monomers spontaneously assemble into insoluble fibrin strands.**

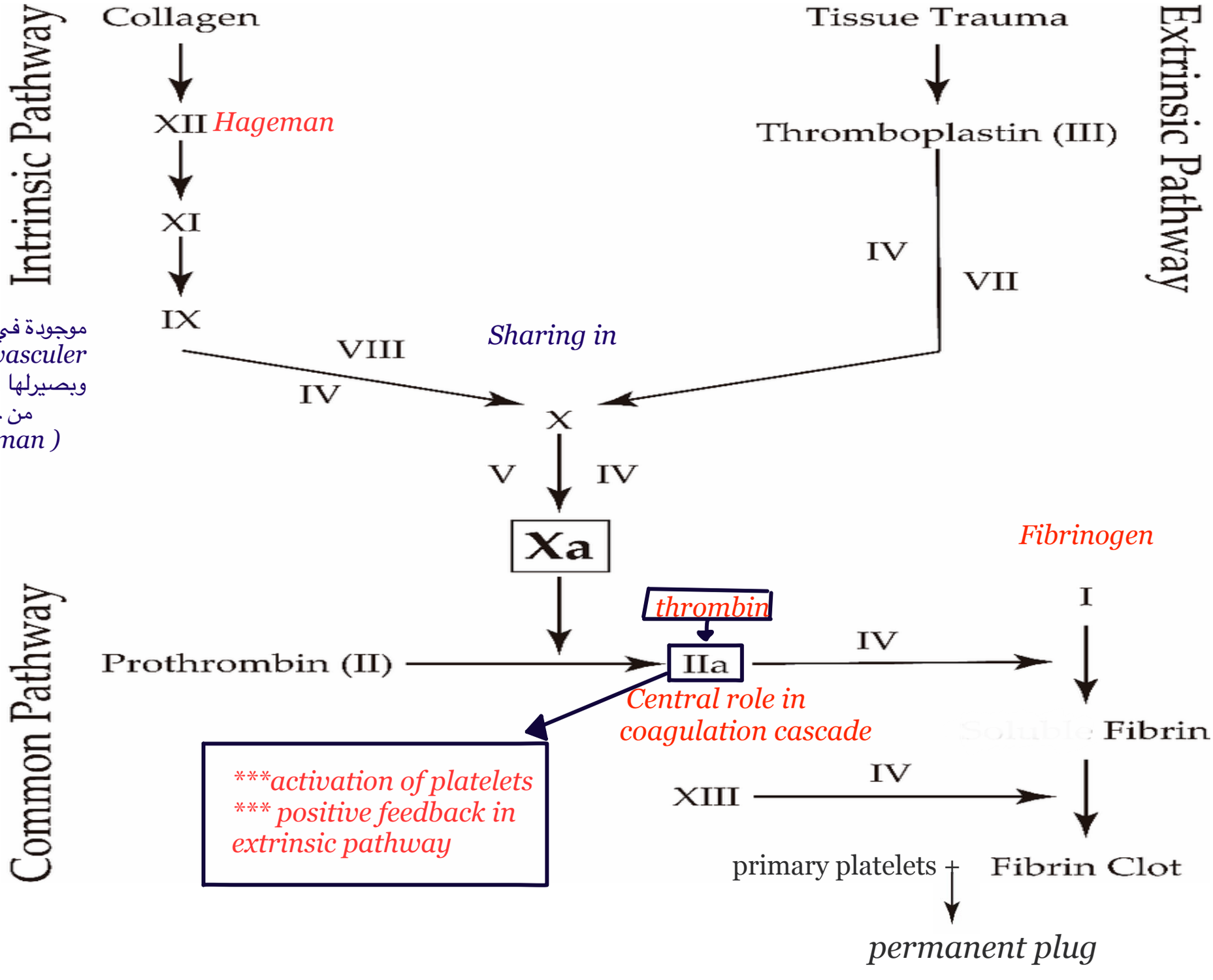
e. Fibrin Binding to Platelet Aggregate:

- **The newly formed fibrin strands bind to the platelet aggregate formed in the primary hemostatic plug.**
- **This binding stabilizes the platelet aggregate and converts the temporary plug into a more permanent structure.**

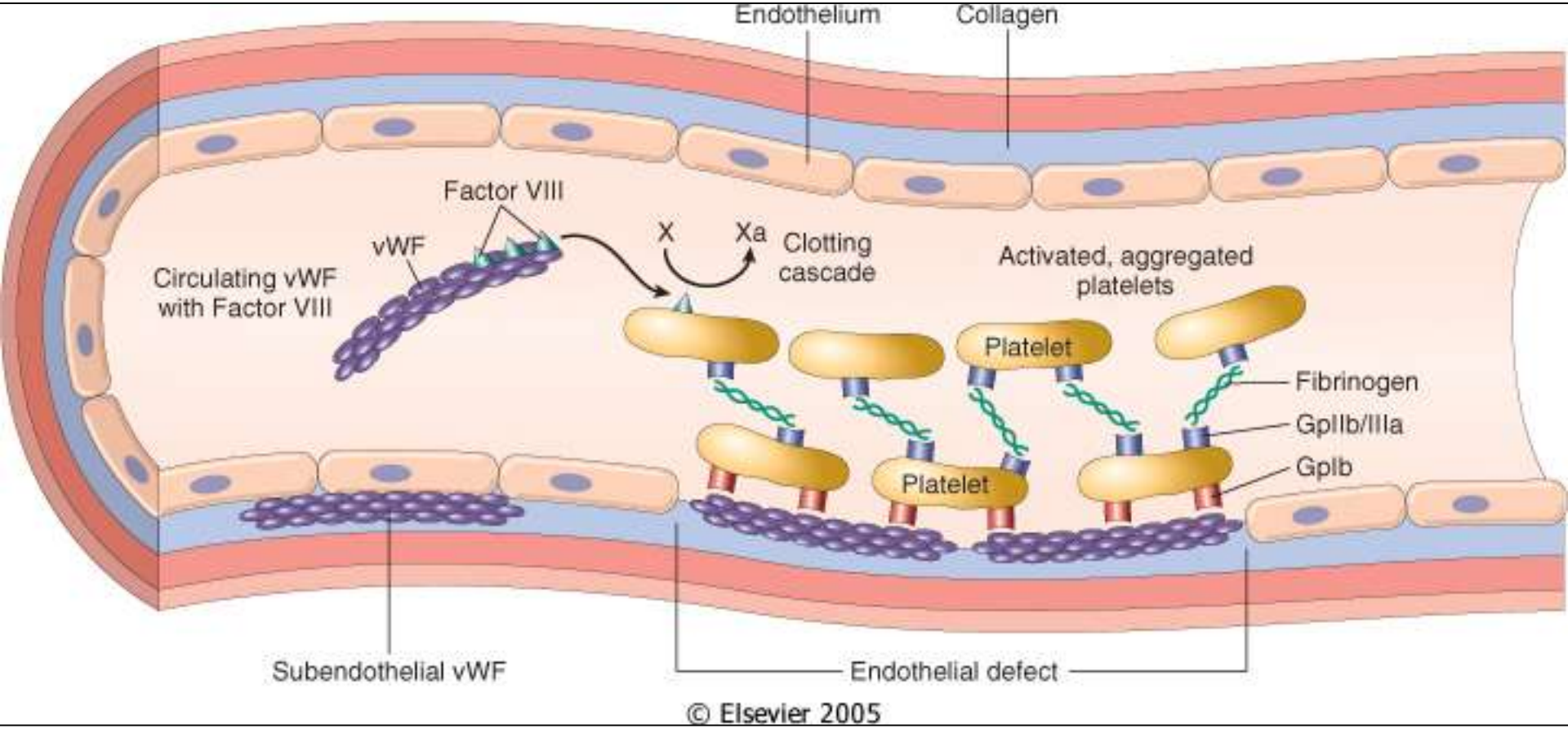
f. Secondary Hemostasis:

- **The entire process, involving the conversion of the primary platelet plug into a stable structure supported by fibrin, is referred to as secondary hemostasis.**

كيف رح يتكون ال *fibrin* ؟



موجودة في ال *intravasculer activation* وبصيرلها *factor* من خلال *XII(Hageman)*



Present in Endothelial Cells

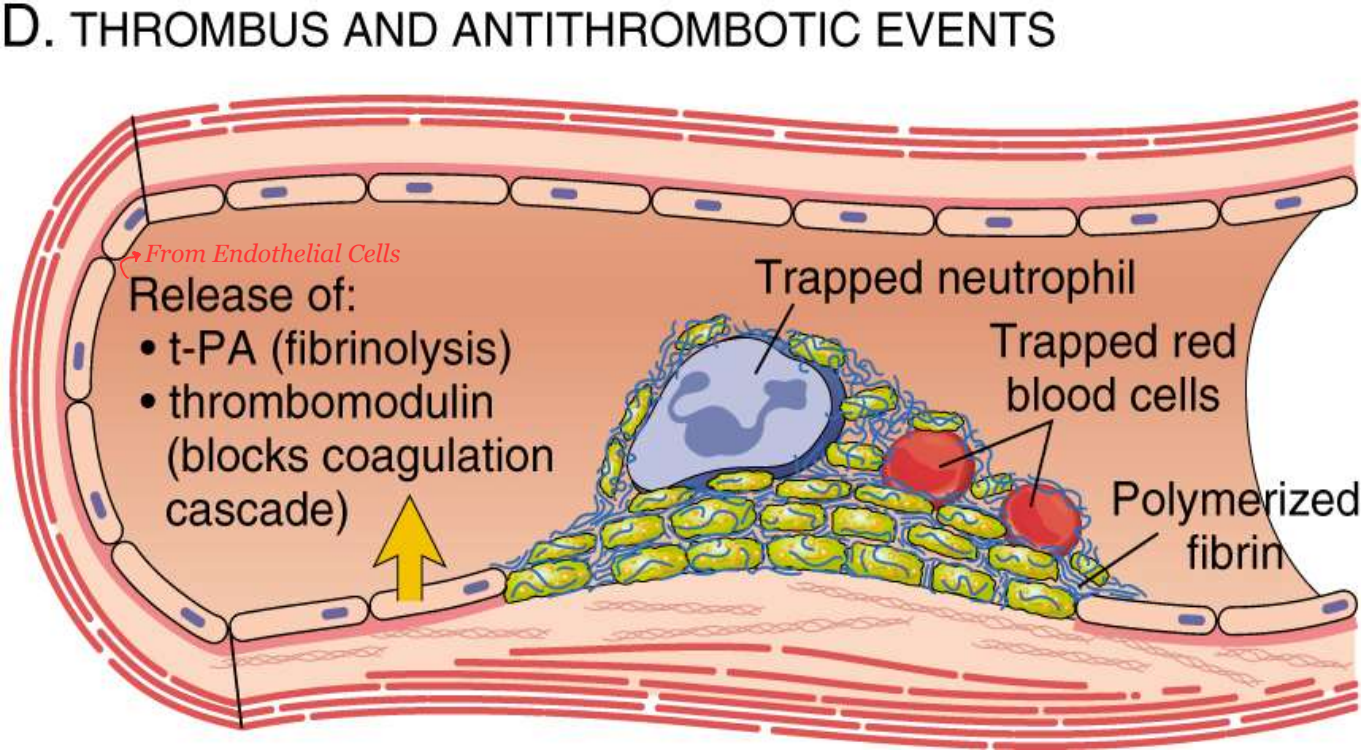
Antithrombotic Functions
Fibrinolytic Effects

After the formation of a blood clot, it is essential to prevent excessive and unnecessary clotting. Fibrinolysis is the process by which clots are dissolved or broken down

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

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

The endothelial cells lining blood vessels synthesize tissue-type plasminogen activator (t-PA)



1. *Fibrinolytic Effect:*
   - *Tissue-Type Plasminogen Activator (t-PA):*
   - *Synthesized by endothelial cells.*
   - *Binds to fibrin in the clot.*
   - *t-PA activates plasminogen attached to fibrin.*
   - *Plasminogen is converted to plasmin.*
   - *Lysis of Fibrin:*
   - *Plasmin breaks down fibrin into smaller fragments (fibrinolysis).*
   - *Clearance of Fibrin Deposits:*
   - *Fibrin degradation products are removed from circulation.*

2. *Confinement of Clot:*
   - *Fibrinolysis prevents excessive clotting by confining the clot to the site of injury.*
   - *Clot remains localized for effective wound healing.*

من هون رح يكون شرح
مفصل نفس يلي انحكى فوق

Endothelium

- *Preventing direct interaction of platelets with the subendothelial ECM.*
- *Producing vasodilators (prostacyclin and nitric oxide) that inhibit platelet aggregation.*
- *Generating ADPase to degrade ADP, further inhibiting platelet activation.*

Antithrombotic Properties of Normal Endothelium:

- **Inhibitory Effects on Platelets:**

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

Inhibitory Effects on Coagulation Factors:

- **The heparin-like molecules**: Activates **antithrombin**
- **Thrombomodulin:** activates **protein C (anticoagulant)**
- **Tissue factor pathway inhibitor** (TFPI)

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.** *Factor 3 and factor 7*
- Endothelial cells produce tissue factor
- **Antifibrinolytic Effects.**
- Activated endothelial cells secrete plasminogen activator inhibitors (PAIs)

تعتبر الحارس لما يصير عنا اي *injury*

Platelets

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

- α granules عبارة عن 300 نوع من البروتين
- Dense bodies (δ granules): contain adenine nucleotides (ADP and ATP), ionized calcium, histamine, serotonin,and epinephrine

شرح خارجي

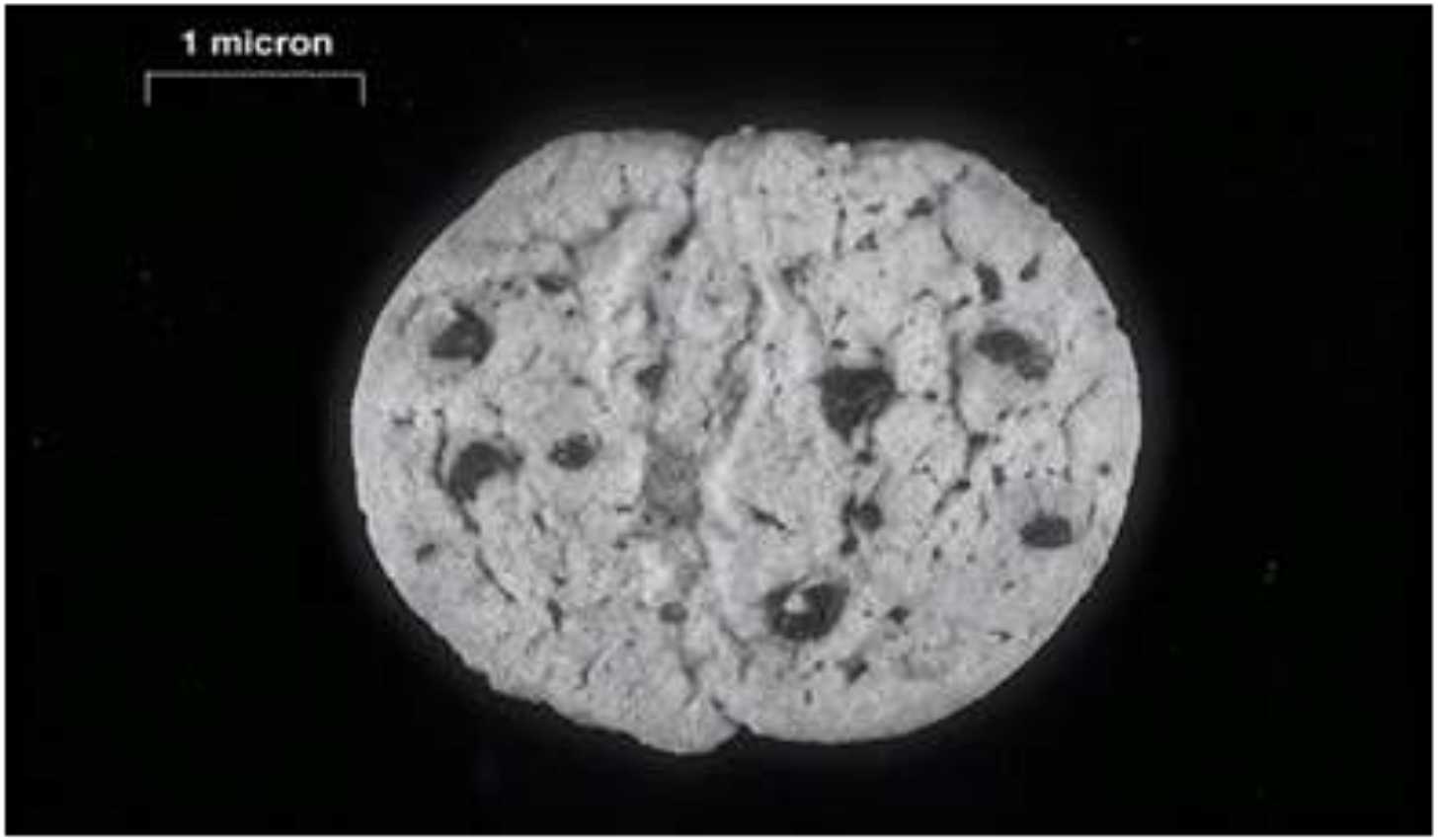
1. *Origin from Megakaryocytes:*
   - *Platelets are tiny, anucleate (lacking a nucleus) cell fragments.*
   - *They are derived from large precursor cells called megakaryocytes, which are found in the bone marrow.*

2. *Formation Process:*
   - *Megakaryocytes undergo a unique process called thrombopoiesis to produce platelets.*
   - *During thrombopoiesis, the megakaryocyte's cytoplasm extends into long, branching projections called proplatelets.*

3. *Proplatelet Formation:*
   - *Proplatelets extend into blood vessels within the bone marrow.*
   - *The shear forces in the bloodstream cause the proplatelets to break into smaller fragments, resulting in the formation of individual platelets.*

4. *Release into the Bloodstream:*
   - *Once formed, platelets are shed into the bloodstream from the marrow megakaryocytes.*
   - *They circulate freely in the blood, playing a crucial role in hemostasis and blood clotting..*

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:

بالوضع الطبيعي ال platelets
تكون مواجهة endothelial
المشكلة لو لامست ال cells
sub endothelial collage
هون معناه في injury

1- Platelet **Adhesion**

موجود على ال damage endothelial cells

هاد الpart من ال platelets
هو رح يمسح مع vWF

- 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**

- Stimulated by TxA2.

جدا قوي اضافة لانه بعمل *vasoconstriction*

- Promoted by bridging interactions between **fibrinogen and GpIIb/IIIa** receptors on adjacent platelets .

موجودة على سطح ال *platelets* بس بتكون في ال *inactive*
فرح يصيرلها *form* و تساعد بالالتصاق ال *activation*
platelets مع بعض و بينهم *fibrinogen*

- Rare inherited deficiency of GpIIb/IIIa (Glanzmann thrombasthenia)

نتيجتها رح يصير عند هاد المريض *bleeding* بدون توقف

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.

تصنع في ال *liver* وتكون في ال *inactive form* r

شرح تحت

- This reaction requires vitamin K as a cofactor

يعتبر vit k عامل أساسي في تكوين γ-Carboxyglutamic Acid (Gla) Residues من خلال اضافة carboxyl groups لل glutamic acid و residues

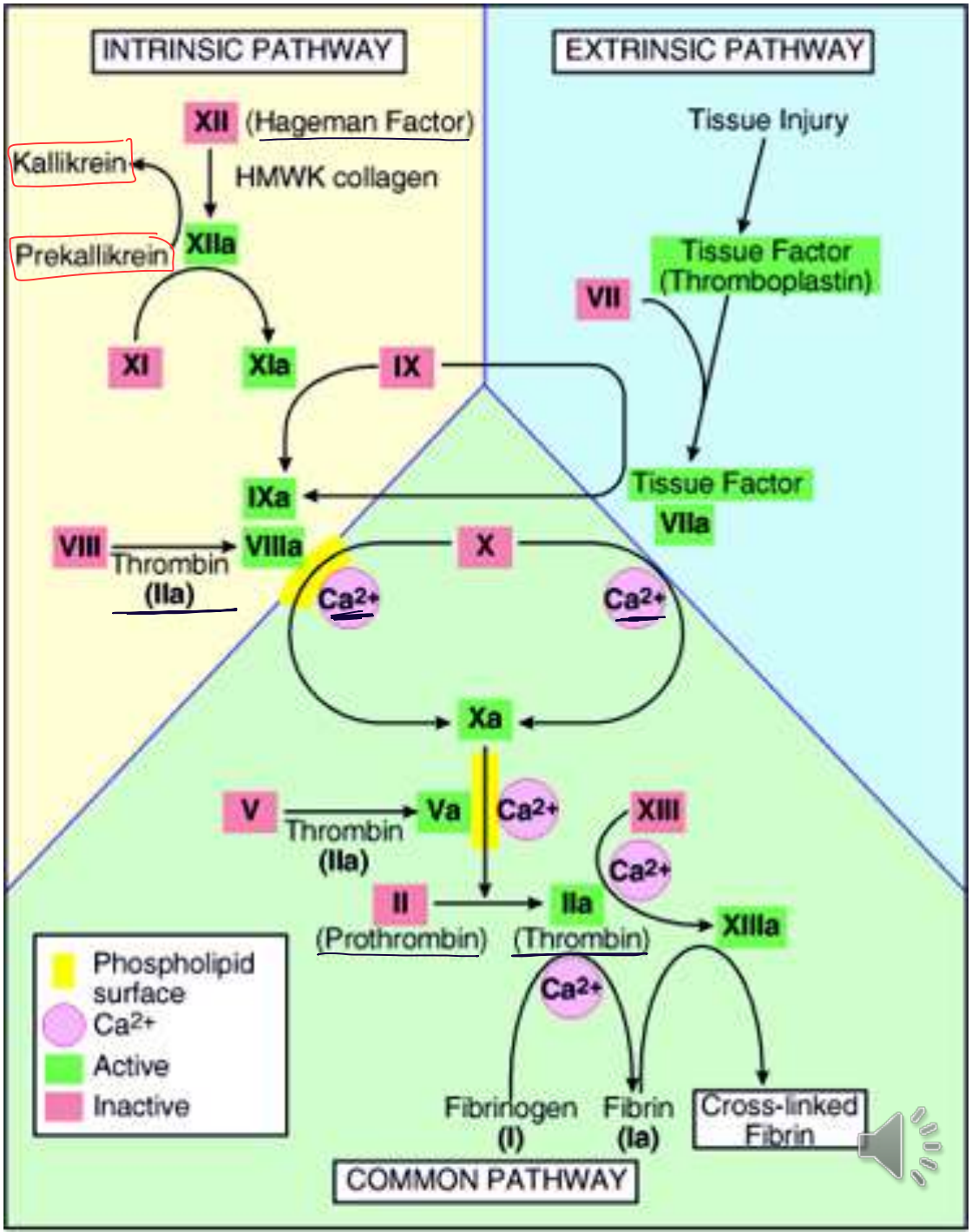
لهذا السبب بعض ال anti coagulation dtuge يستهدفوا vit k

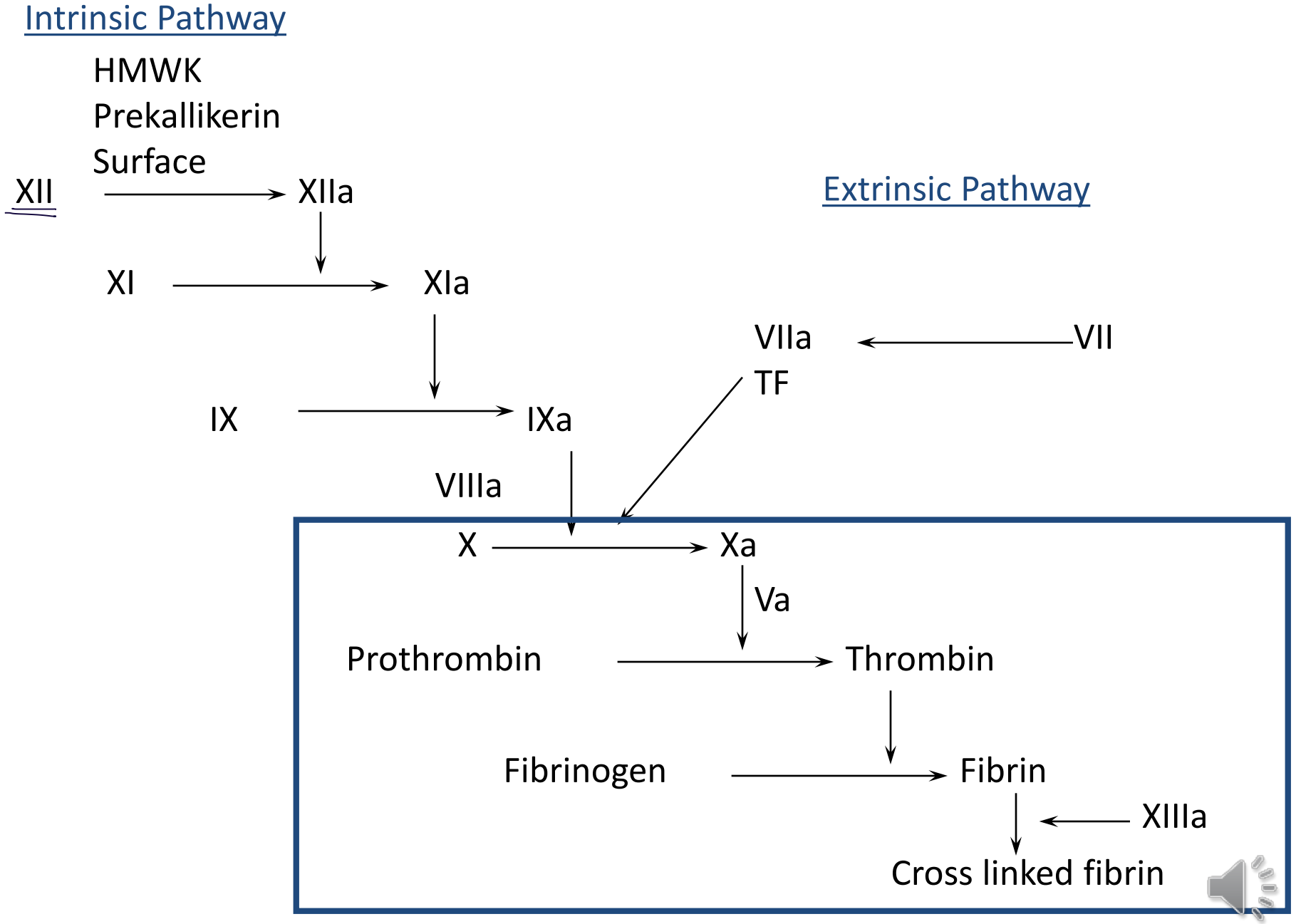
- Blood coagulation divided into **extrinsic** and **intrinsic** pathways, converging at the **activation of factor X** .
- Several interconnections between the two pathways exist.
- The **extrinsic** pathway is the most physiologically relevant pathway for coagulation occurring after vascular damage;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

الصور بتفاصيلهم مطلوبة :)

The coagulation cascade

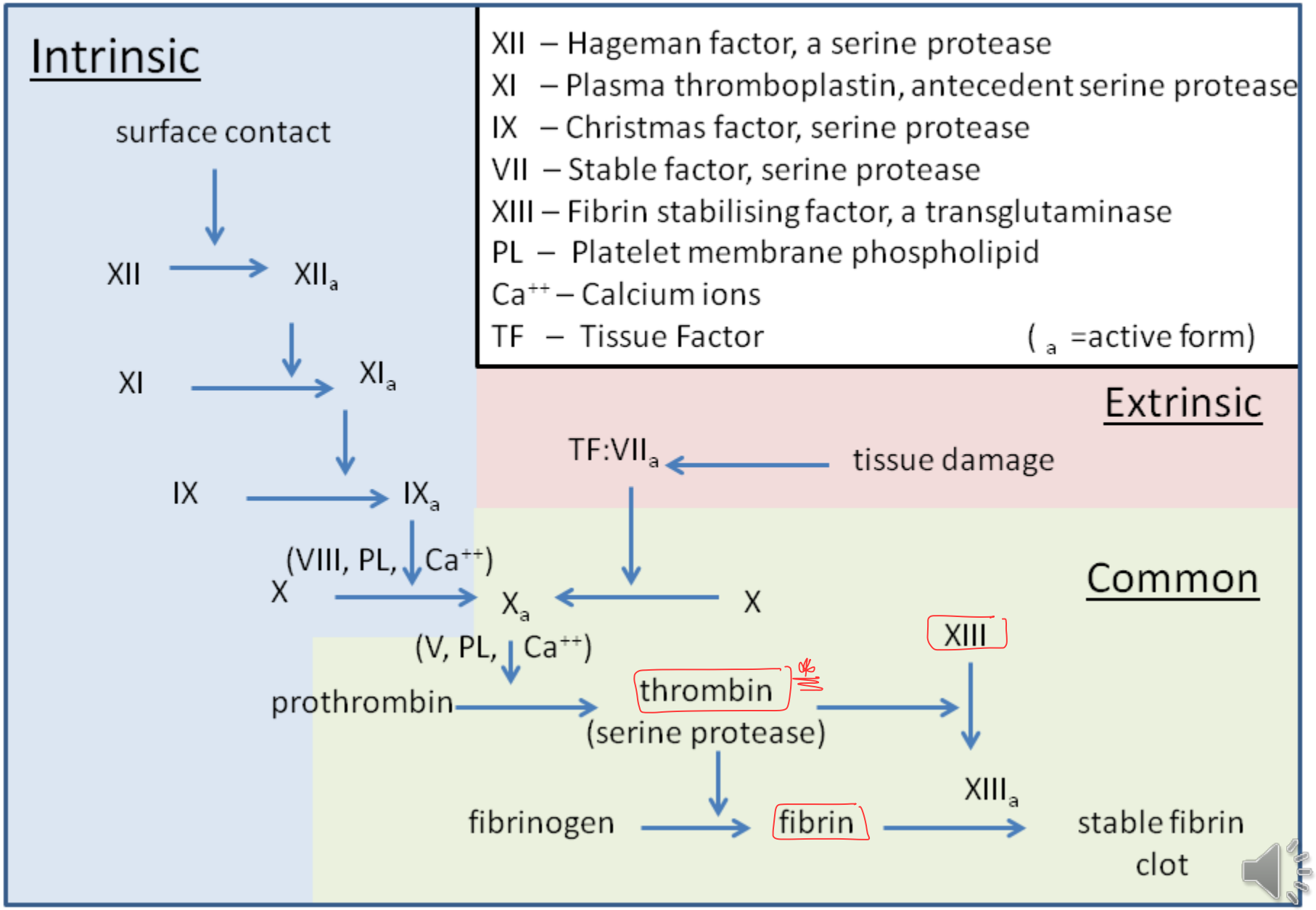
- Factors in red boxes represent inactive molecules.
- Activated factors are indicated with a lower case "a" and a green box.
- HMWK (high molecular weight kininogen).




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

هاي الصورة أوضح اعتمدوها

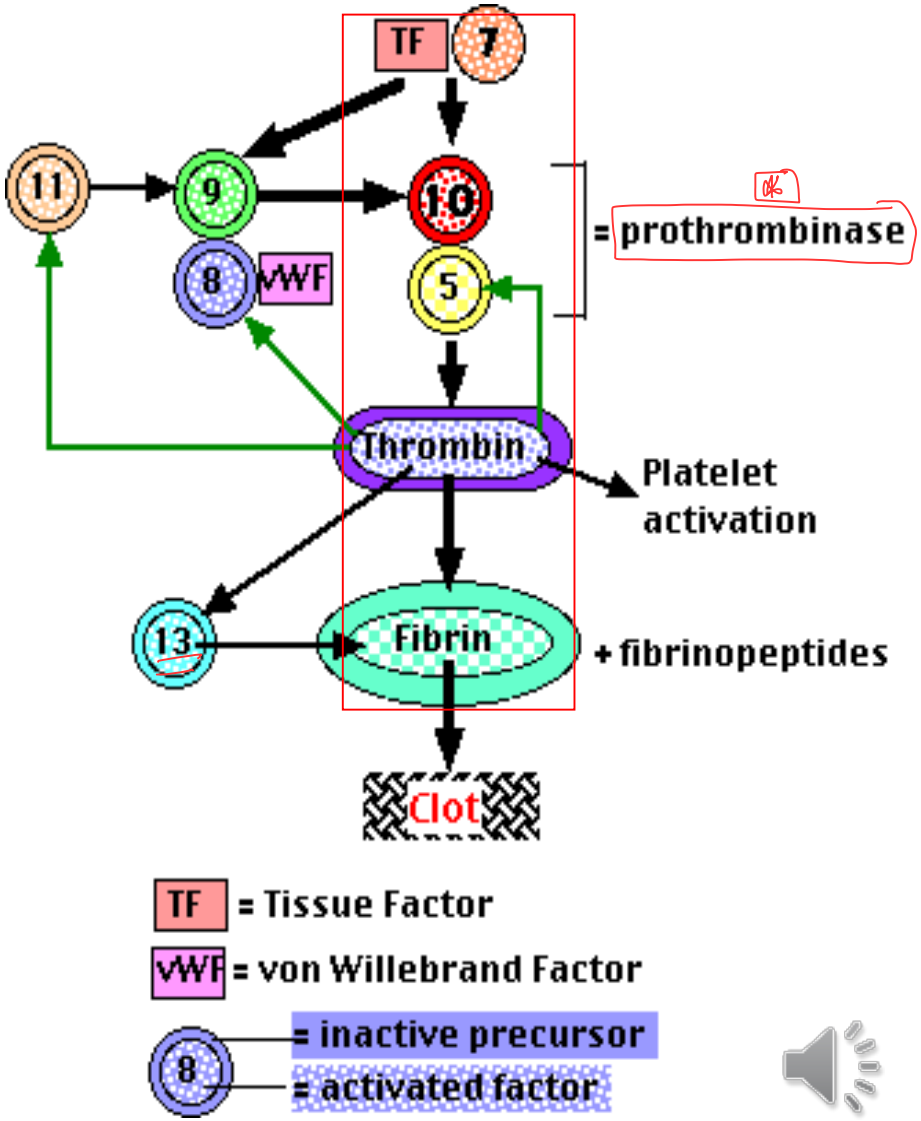
The three pathways that makeup the classical blood coagulation pathway



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

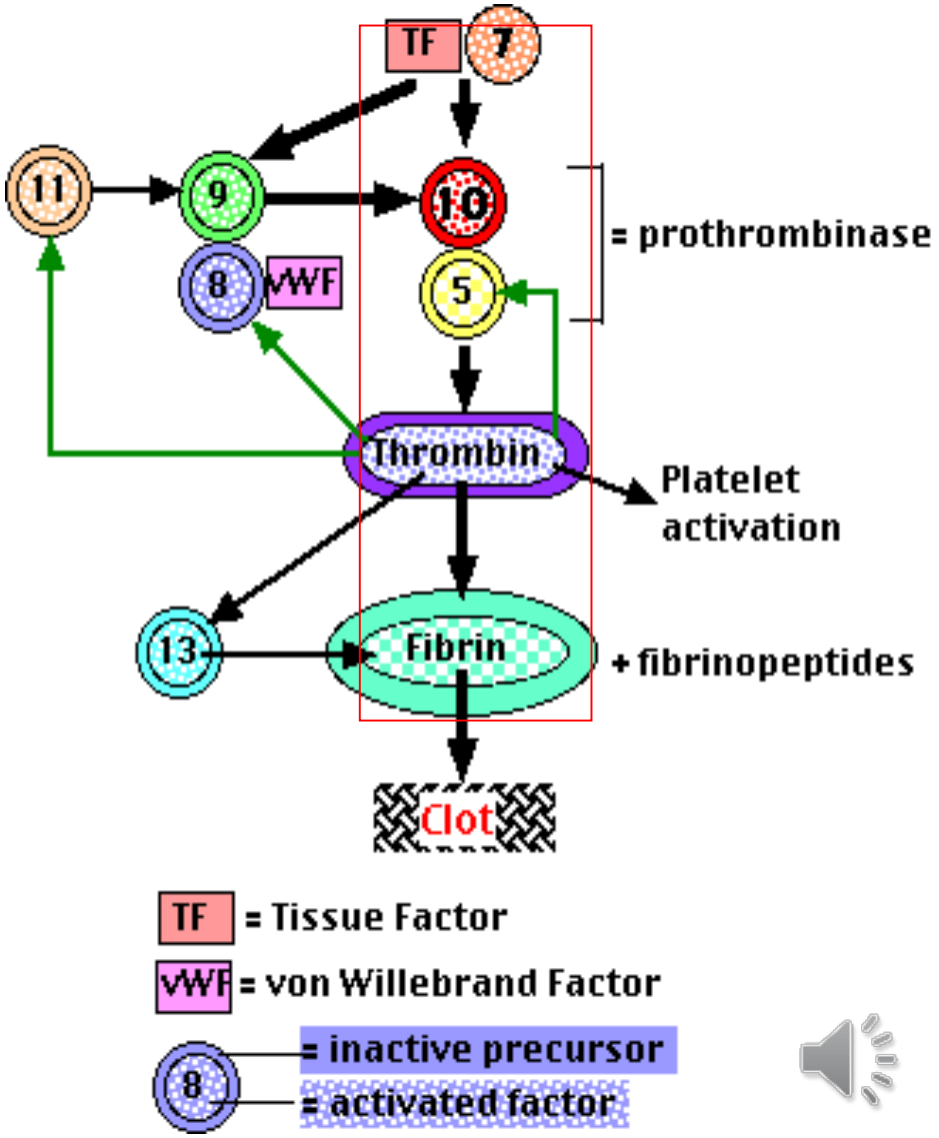
2. Factor 10 binds and activates Factor 5 (prothrombinase) converting prothrombin (also known as Factor II) to thrombin



Coagulation cascade

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

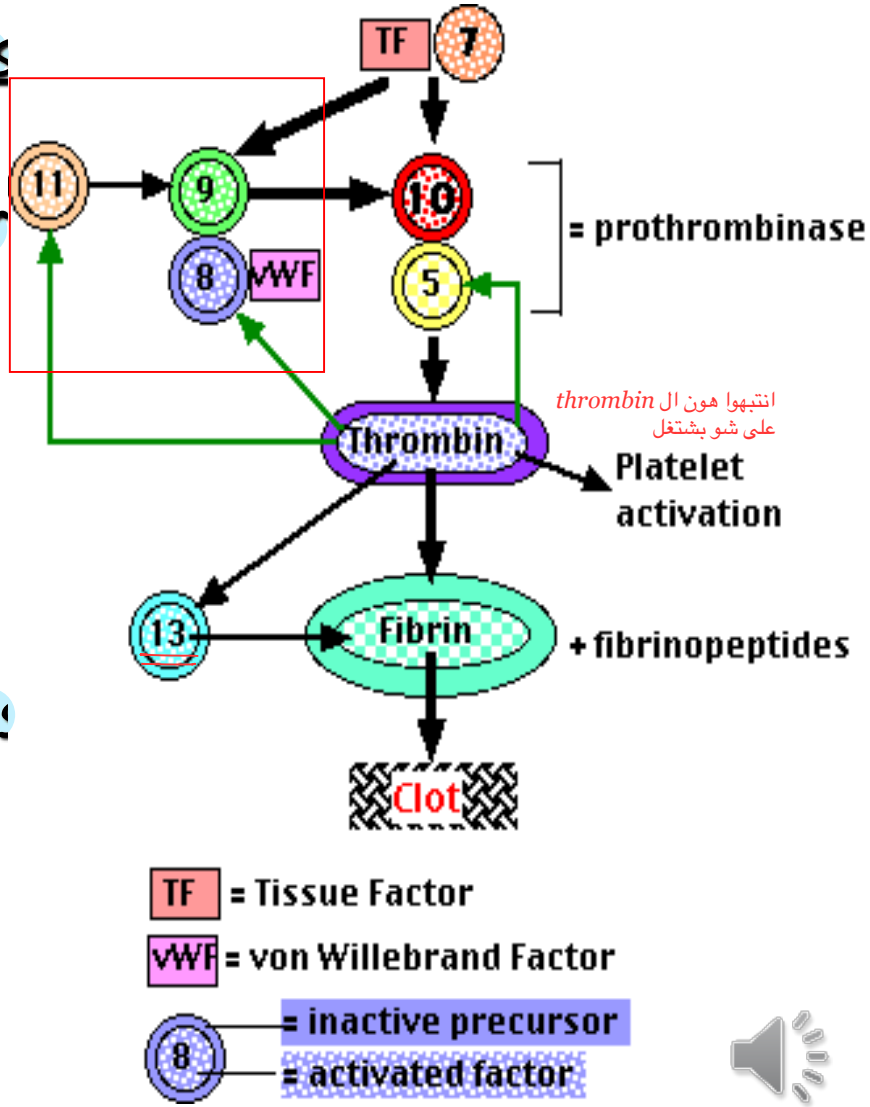
4. Factor 13 forms covalent bonds between the soluble fibrin molecules converting them into an insoluble meshwork — the clot.



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



Coagulation factors and related substances

مهم نعرفهم كلهم

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)

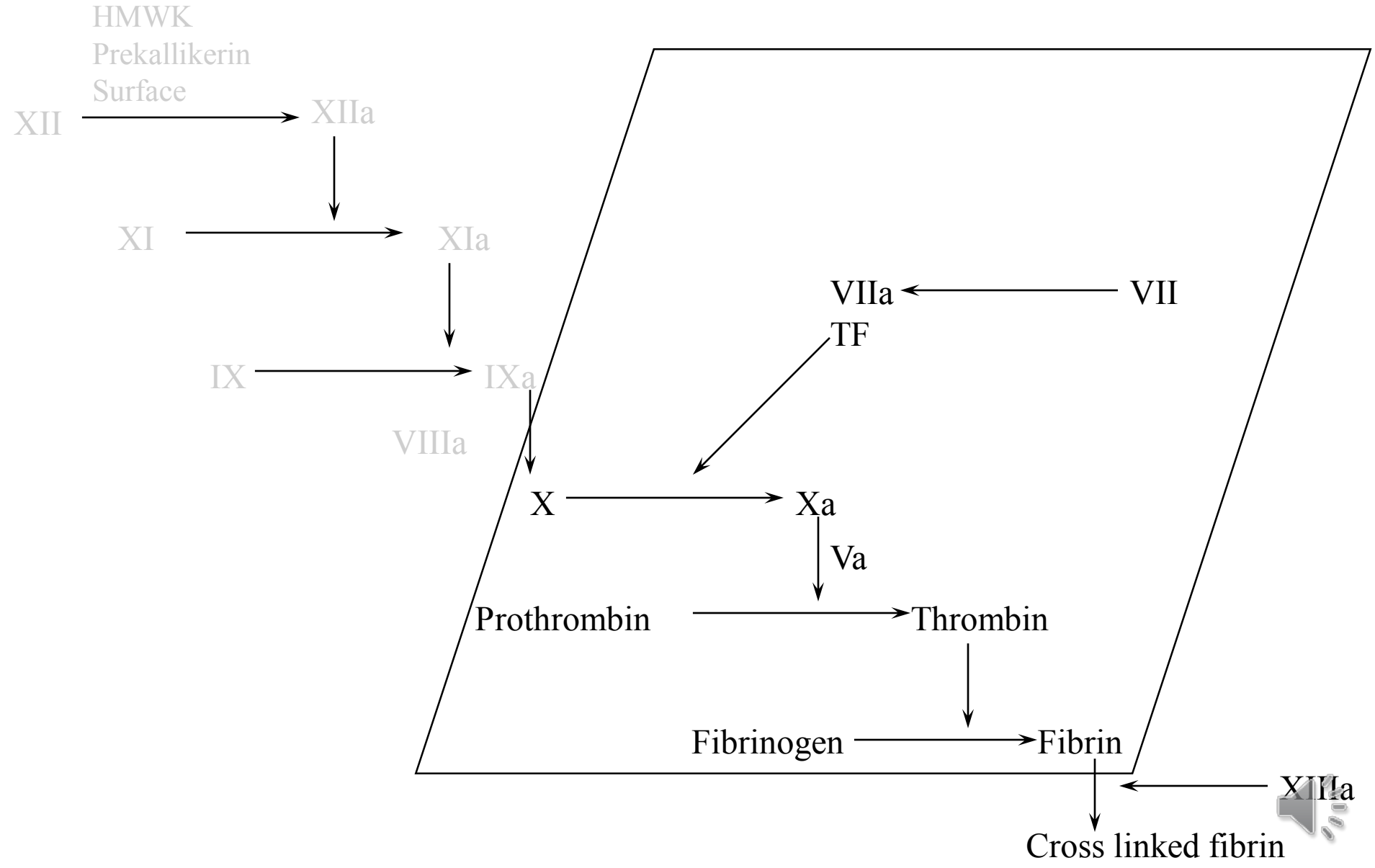
Clinical labs assessment

- **Prothrombin time (PT):**

Clinical Significance:
- *Monitors anticoagulant therapy effectiveness and assesses liver function.*

- 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.

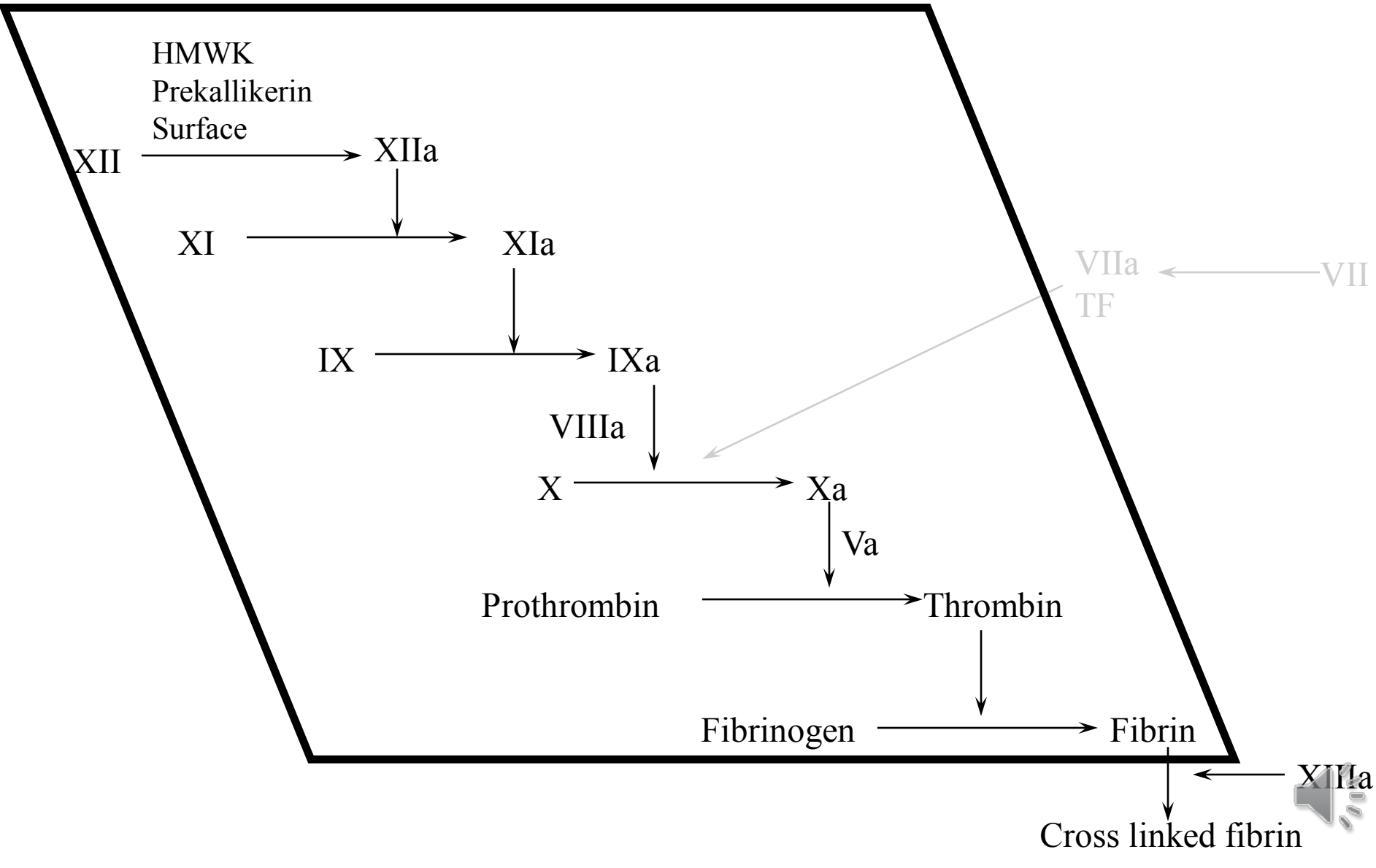
Prothrombin Time(PT)



- **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).
- 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).

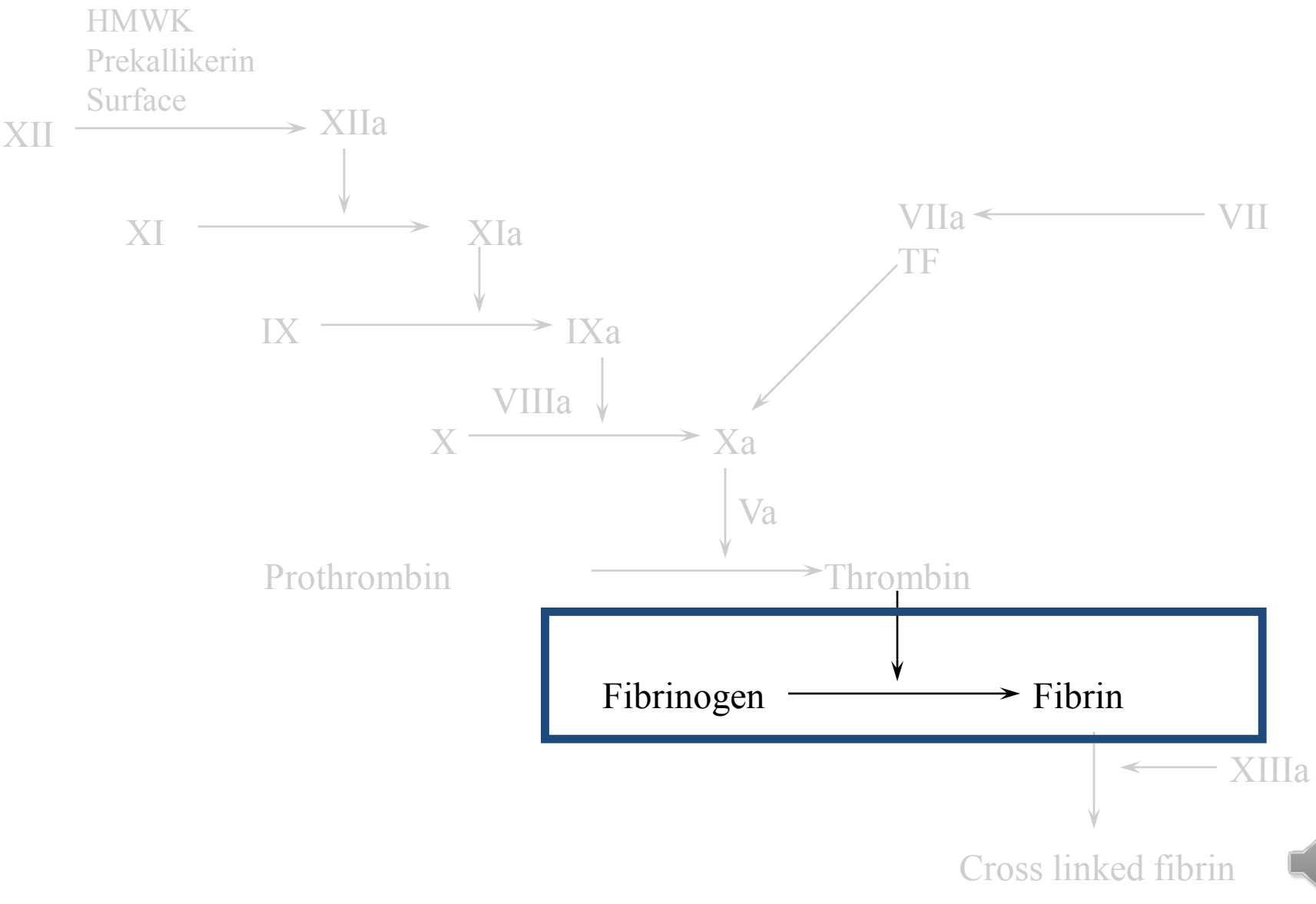
Partial Thromboplastin Time



- **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**

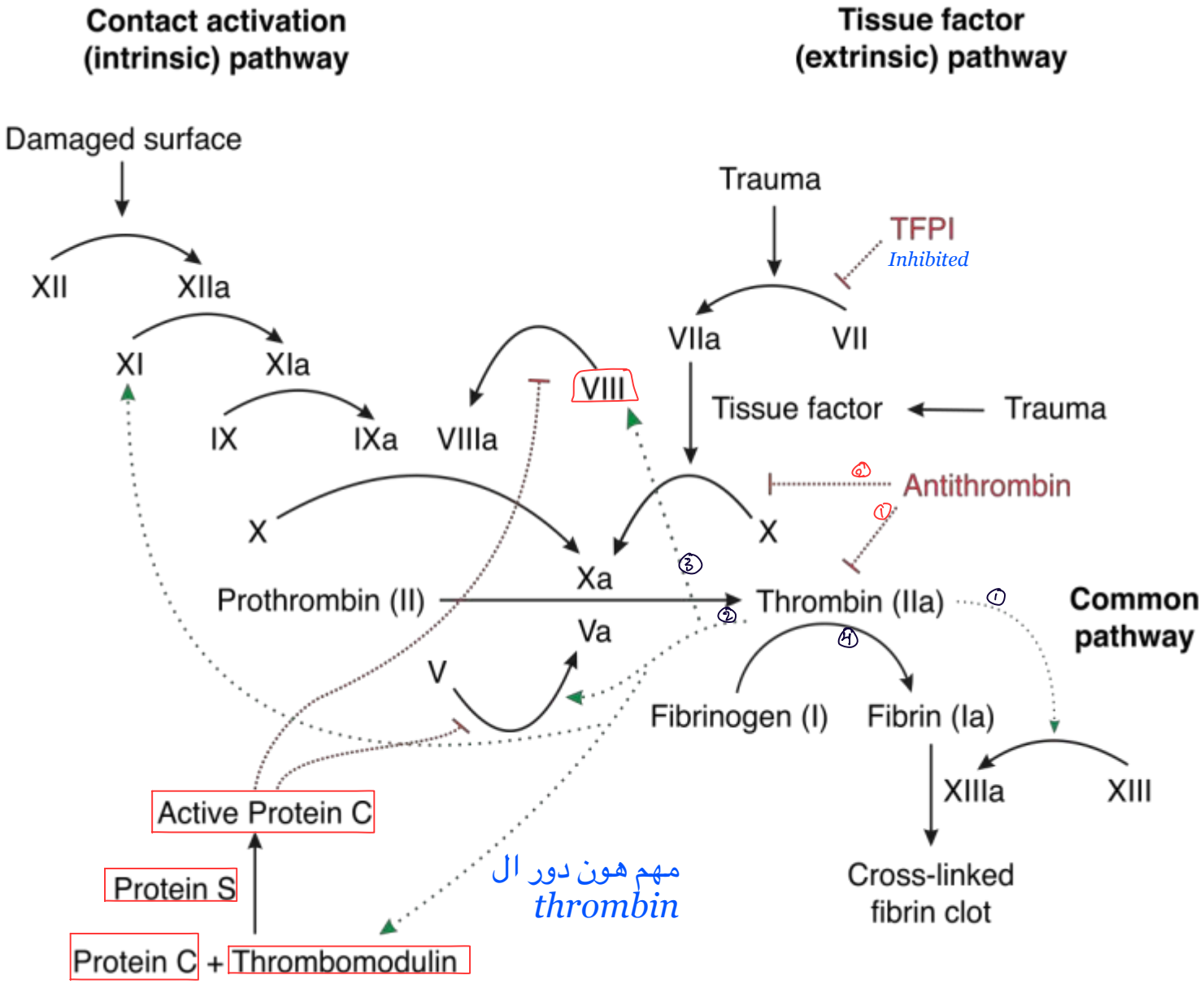
2- Protein C and protein S:

- 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

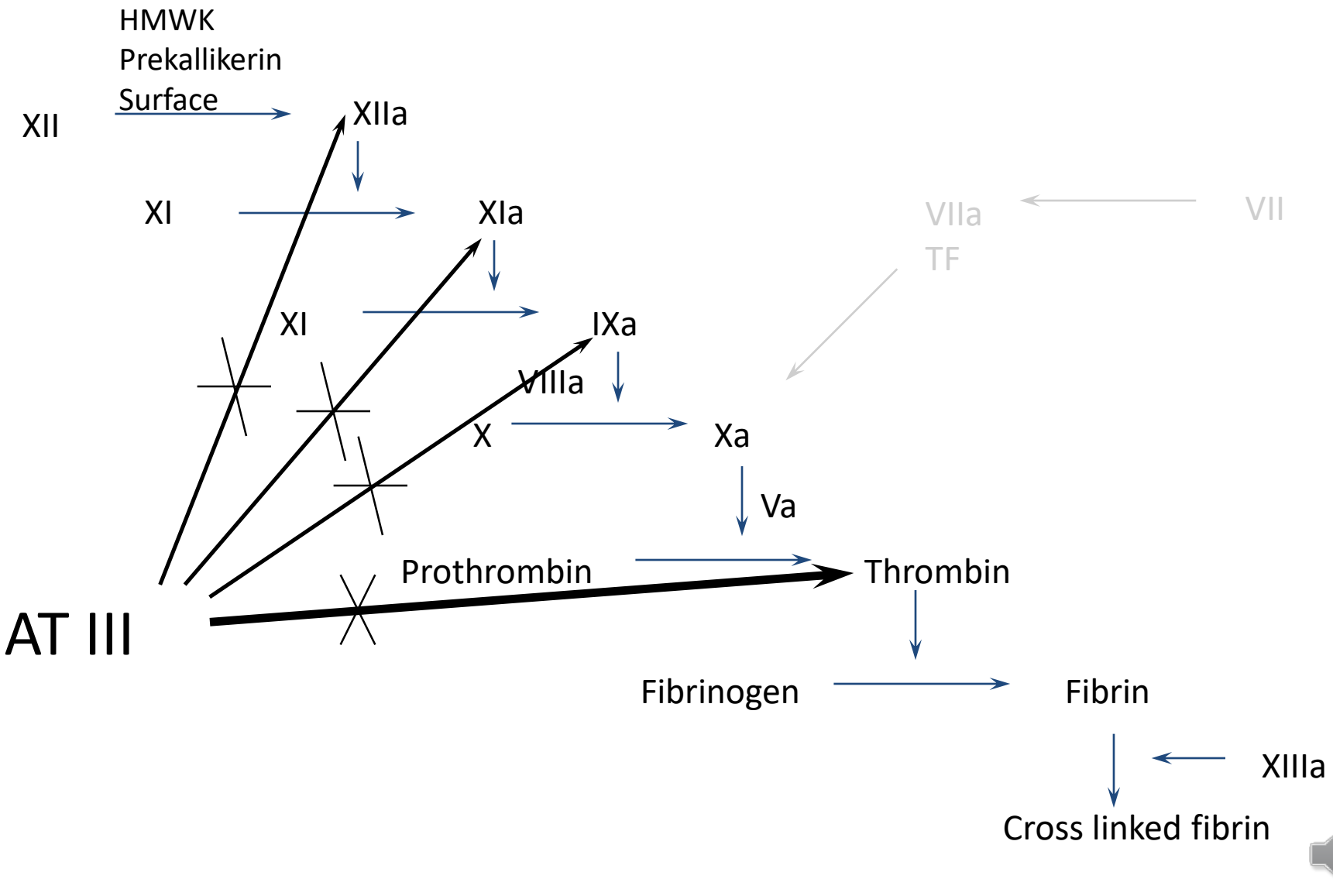
3-Tissue factor pathway inhibitor (TFPI):

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

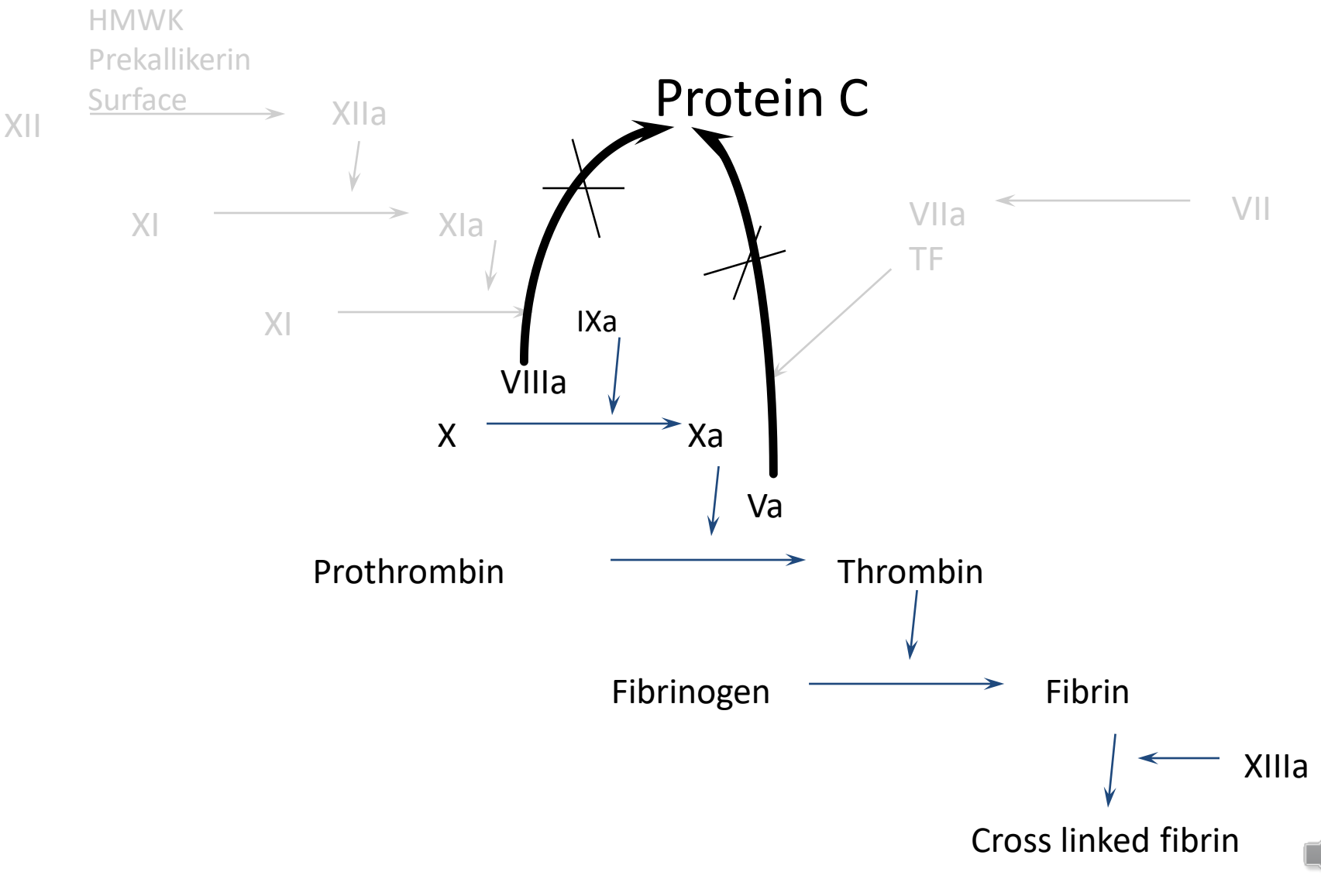
4- Plasmin *plasmin regulates clotting through its role in fibrinolysis. It is activated at the site of a clot, breaks down fibrin strands, generates fibrin degradation products, and contributes to the controlled clearance of the clot.*


Contact activation
(intrinsic) pathway
Tissue factor
(extrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VIII
Trauma
TFPI
Inhibited
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
مهم هون دور ال
thrombin

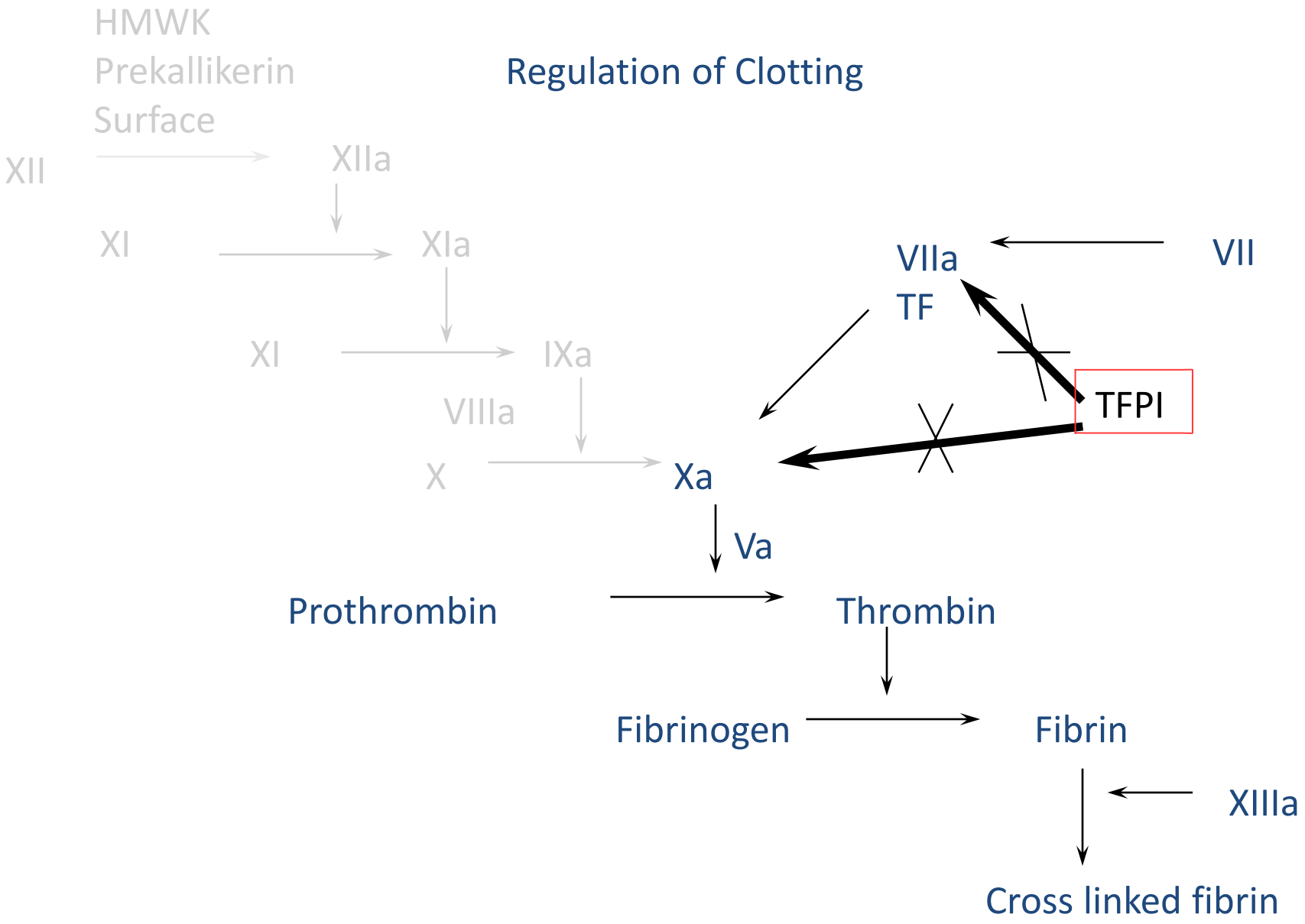
Antithrombin III



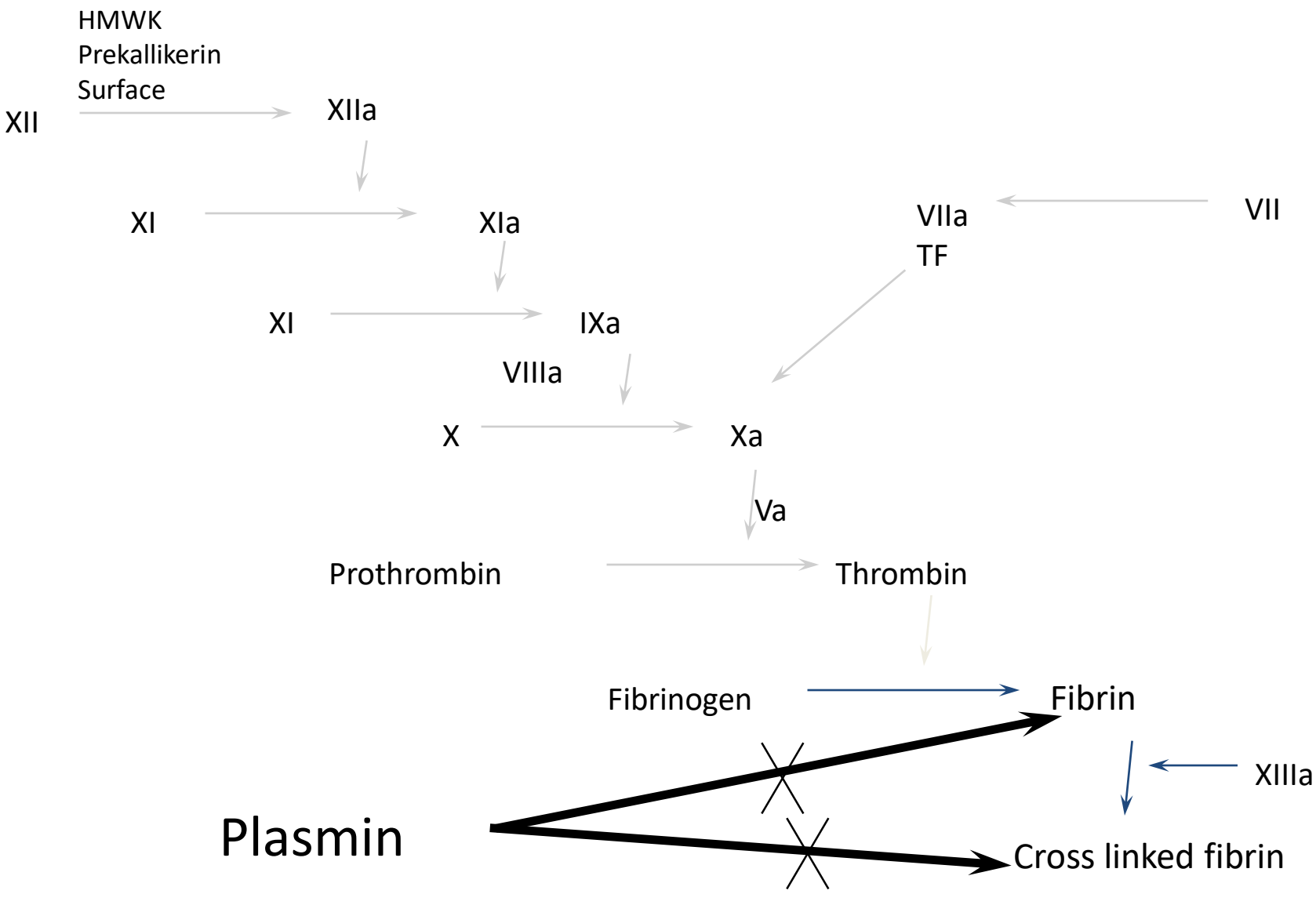
Protein C


HMWK
Prekallikerin
Surface
XII
XIIa
XI
XIa
XI
IXa
VIIIa
X
Xa
Va
Protein C
VIIa
TF
VII
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIIIa
Cross linked fibrin

Regulation of Clotting



Plasmin


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

Regulation of Clotting