Pathology

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التفريغ:براء صافي/حياة&ندى خليفات/وريد

التدقيق: براء صافي

Lec 18

Hemodynamics

Dr. Dua Abuquteish

Hemostasis and Thrombosis

بدنا ال blood يضل fluid ال clot ممكن تسبب ischemia

- 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.
- 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.

Cause ischemia

Thrombus: platelet + fibrine

Clot: fibrine + RBC

الموضوع المحاضروة هو كيف نسكر ال vascular injury

Hemostasis

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

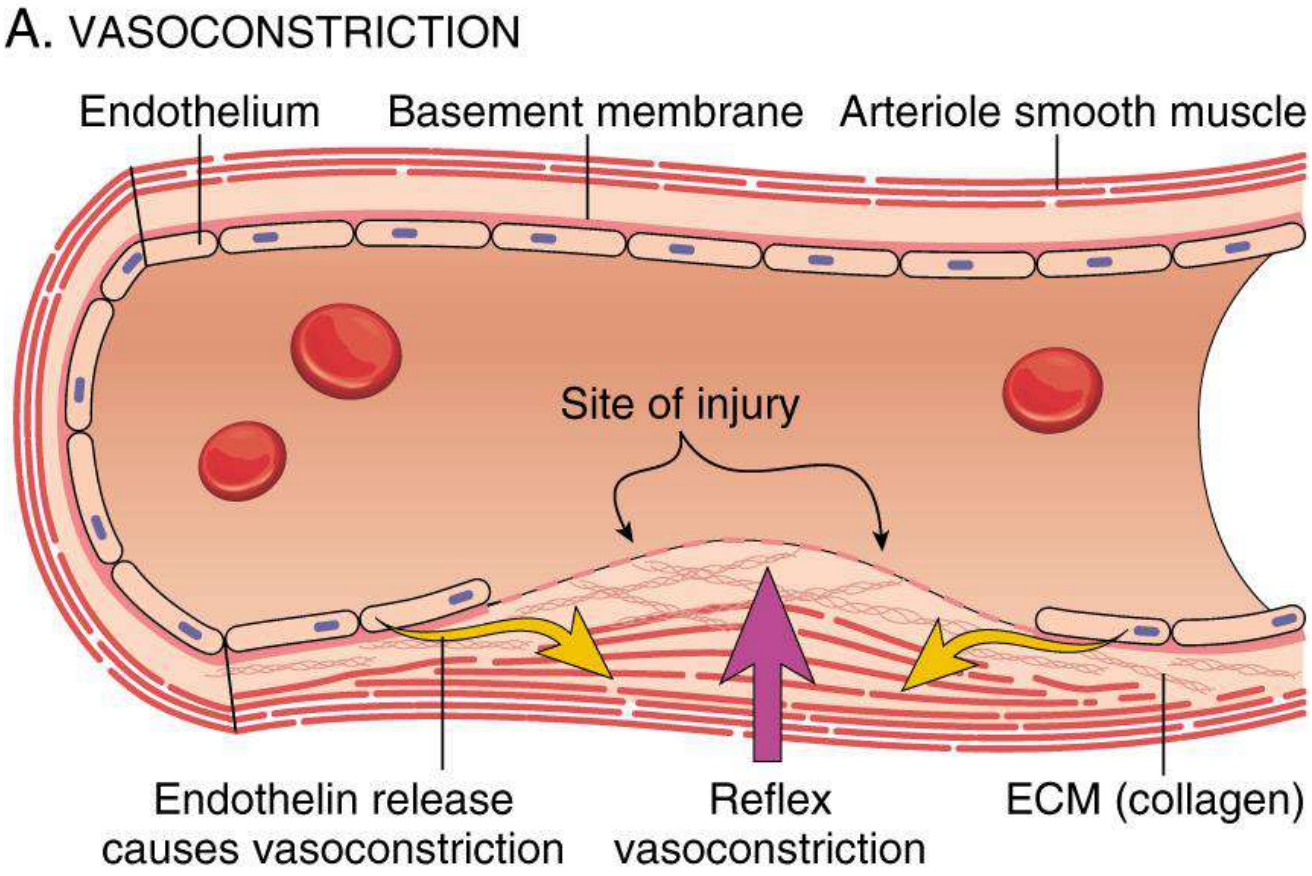
PGI2 and NO prevent platelets from clotting when there is no injury

STEPS IN HEMOSTASIS

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

Endothelin release is the first thing to happen and it causes vc

To ⬇️ bleeding

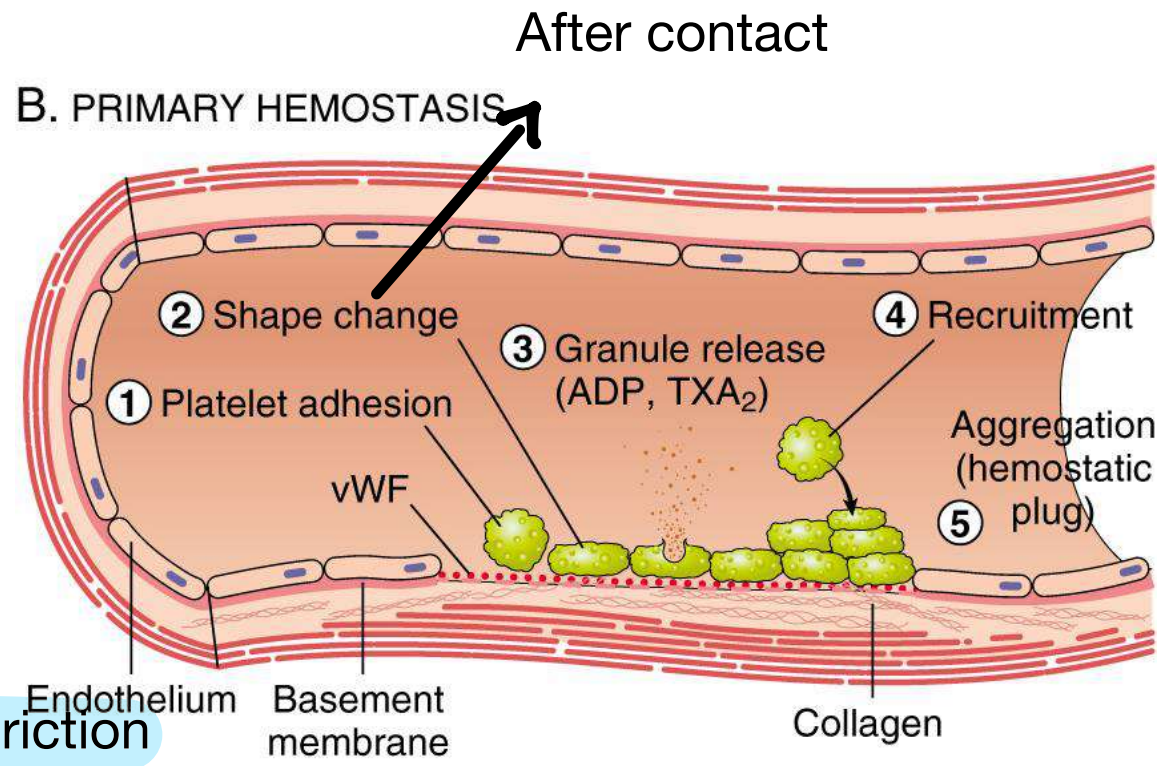


- Platelets are attached to Subendothelial collagen

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 (primary hemostasis)



+vasoconstriction → On smooth muscle

The hemostatic plug is weak that's why its called primary

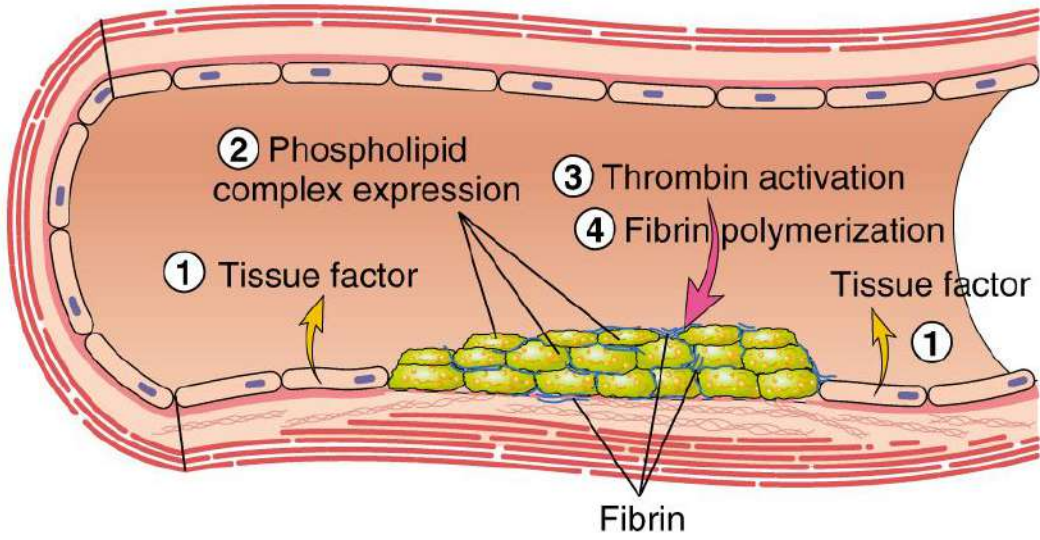
STEPS IN HEMOSTASIS

(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**.

Factor 3

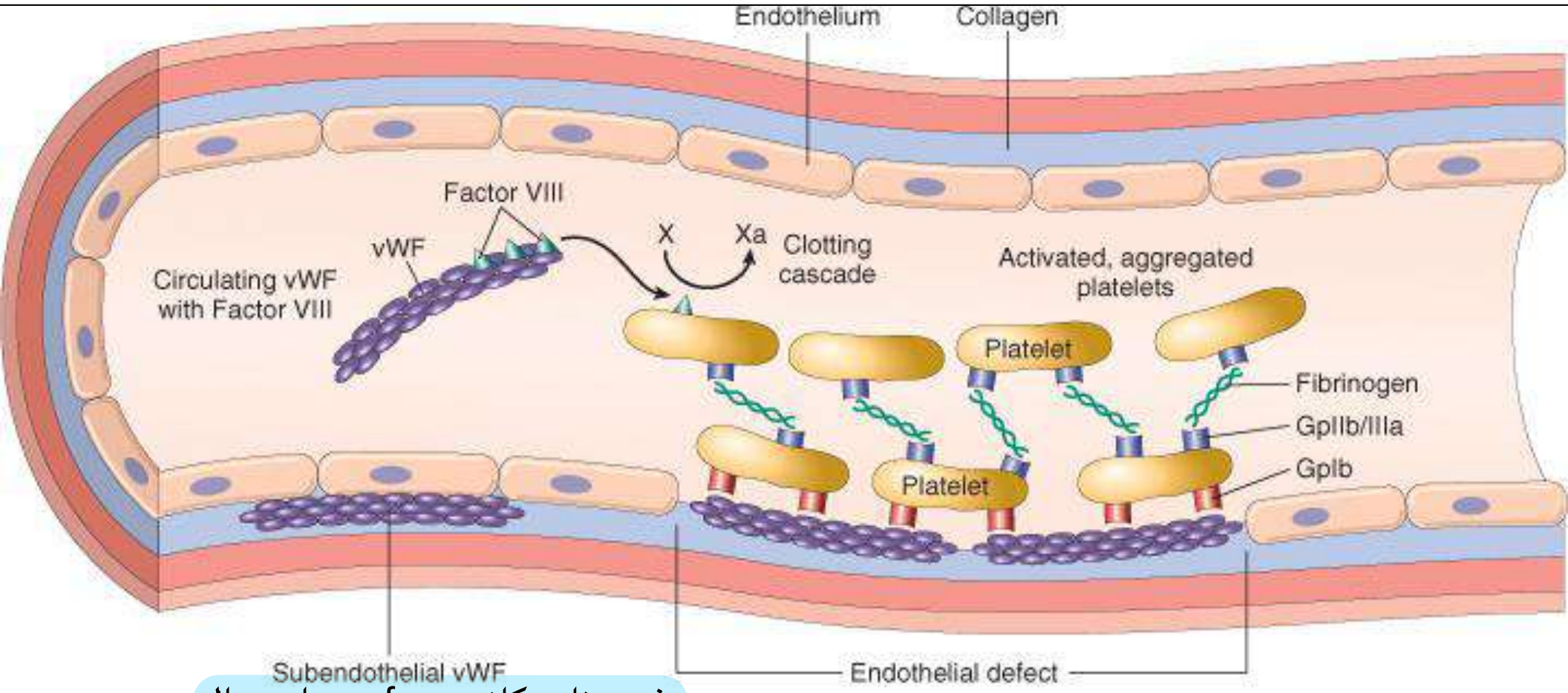
C. SECONDARY HEMOSTASIS



Platelet plug+fibrin mesh
Prevents it from moving

Prothrombin—> thrombin it activates fibrinogen and converts it to fibrin which stimulates platelet aggregation

Vwf (subenodothelial) attaches to platelets through GP1b this changes its shape and induces it to secrete ADP and TxA2 this recruits more platelets to bind to GP11B and and Fibrinogen—> fibrin



في عنا بمكانين من vwf واحد بال blood مرتبط ب factor8 حتى يطول عمره والتاني subenothelial

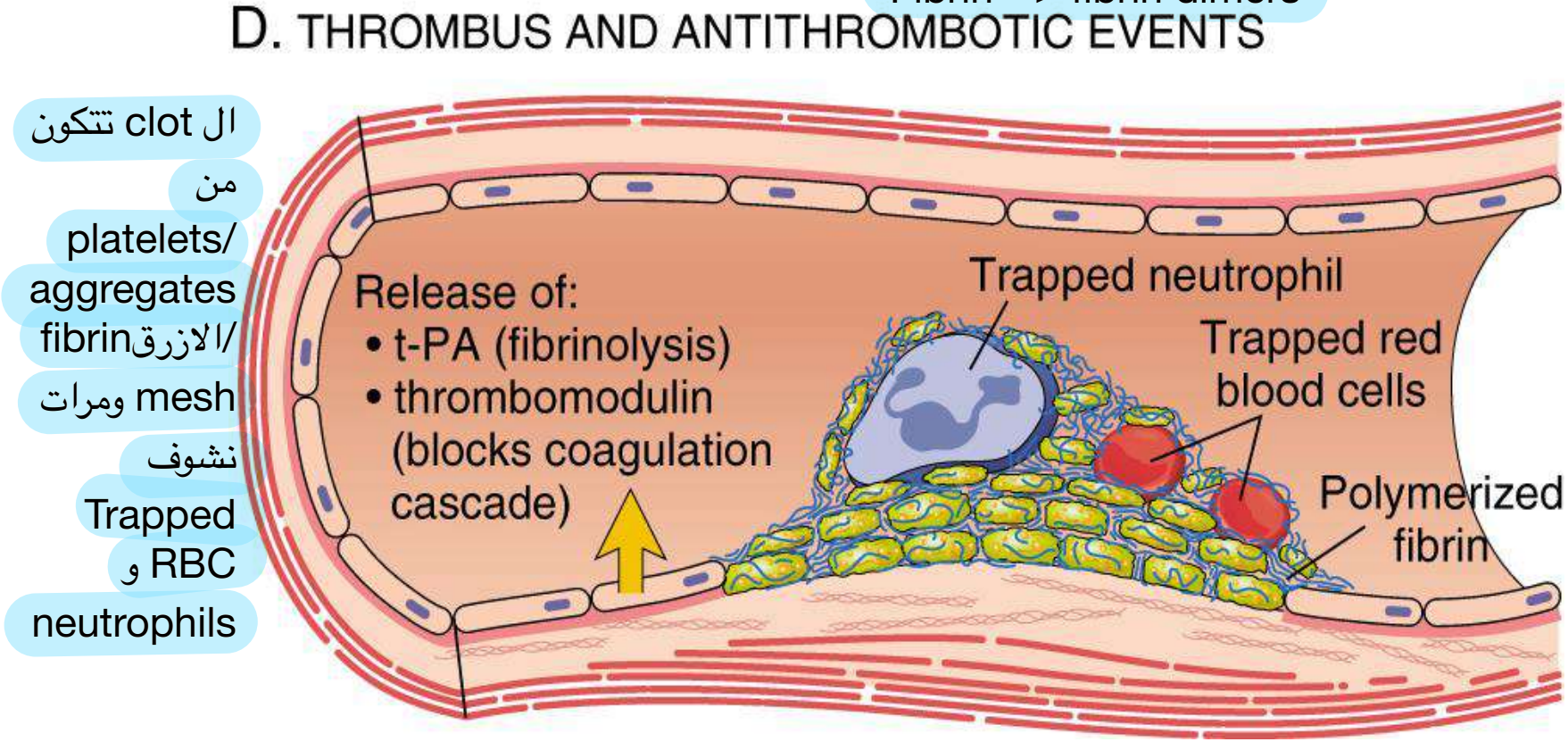
Antithrombotic Functions
Fibrinolytic Effects

(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.

Plasmonogen ->plasmin

Fibrin—> fibrin dimers



ال clot تتكون من platelets/ aggregates الازرق/fibrin ومرات mesh نشوف Trapped و RBC neutrophils

Endothelium

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) → Prevents platelets aggregation

Inhibitory Effects on Coagulation Factors:

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

Extrinsic pathway
TFPI is factor 3

Prevents the action of factor 5 and 8

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.** 3

- Endothelial cells produce tissue factor

- **Antifibrinolytic Effects.** When i want fibrin

- Activated endothelial cells secrete plasminogen activator inhibitors (PAIs)

Until fibrin reaches its maximum amount of the fibrin thats needed

Platelets

لا تحتوي على نواة

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

- α granules ← vwf
- Dense bodies (δ granules): contain adenine nucleotides (ADP and ATP), ionized calcium, histamine, serotonin,and epinephrine

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

Calcium is very imp in the coagulation pathway

This recruits more platelets

After vascular injury:

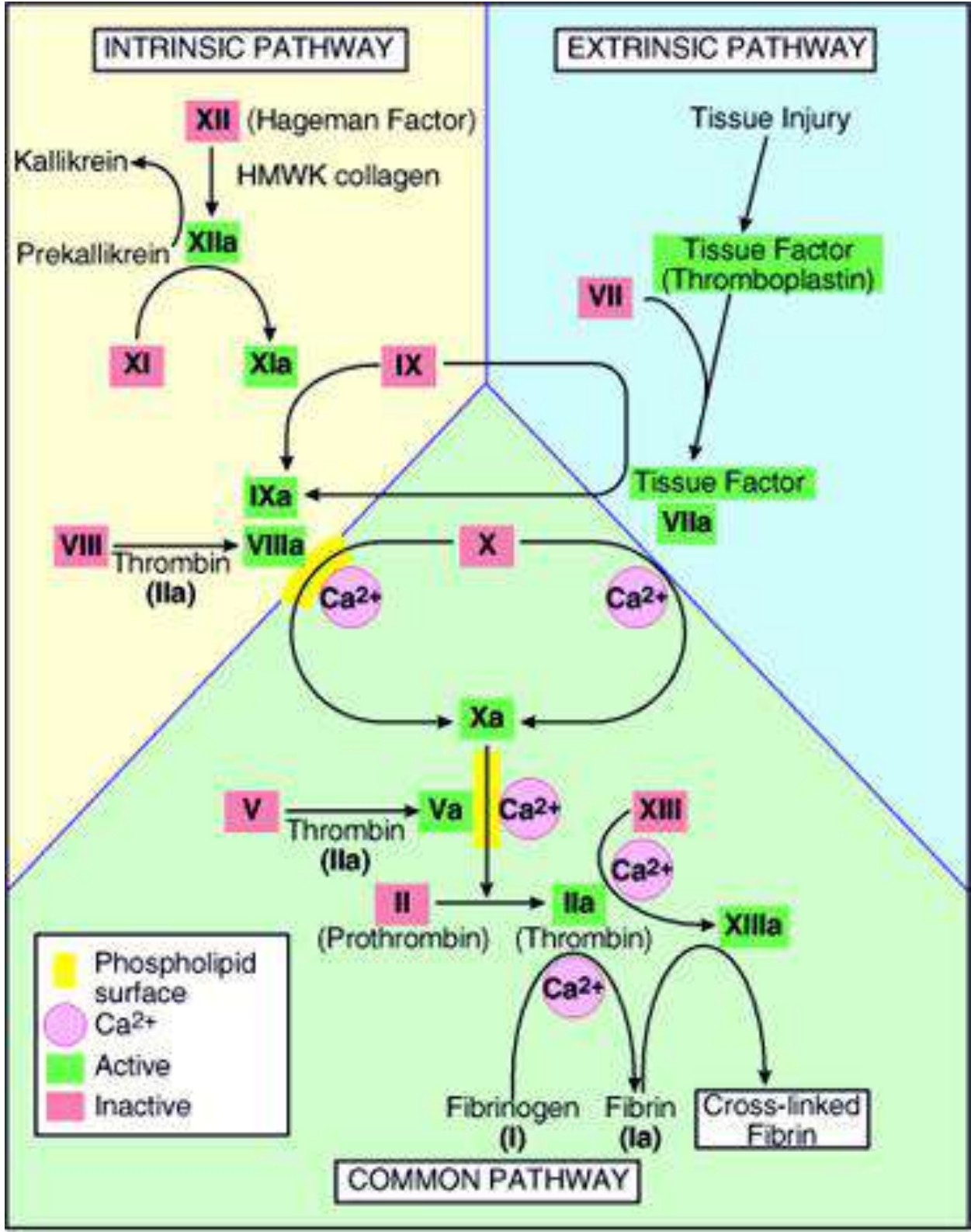
3- Platelet **Aggregation**

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

لو انجرح المريض
يصير bleeding

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).

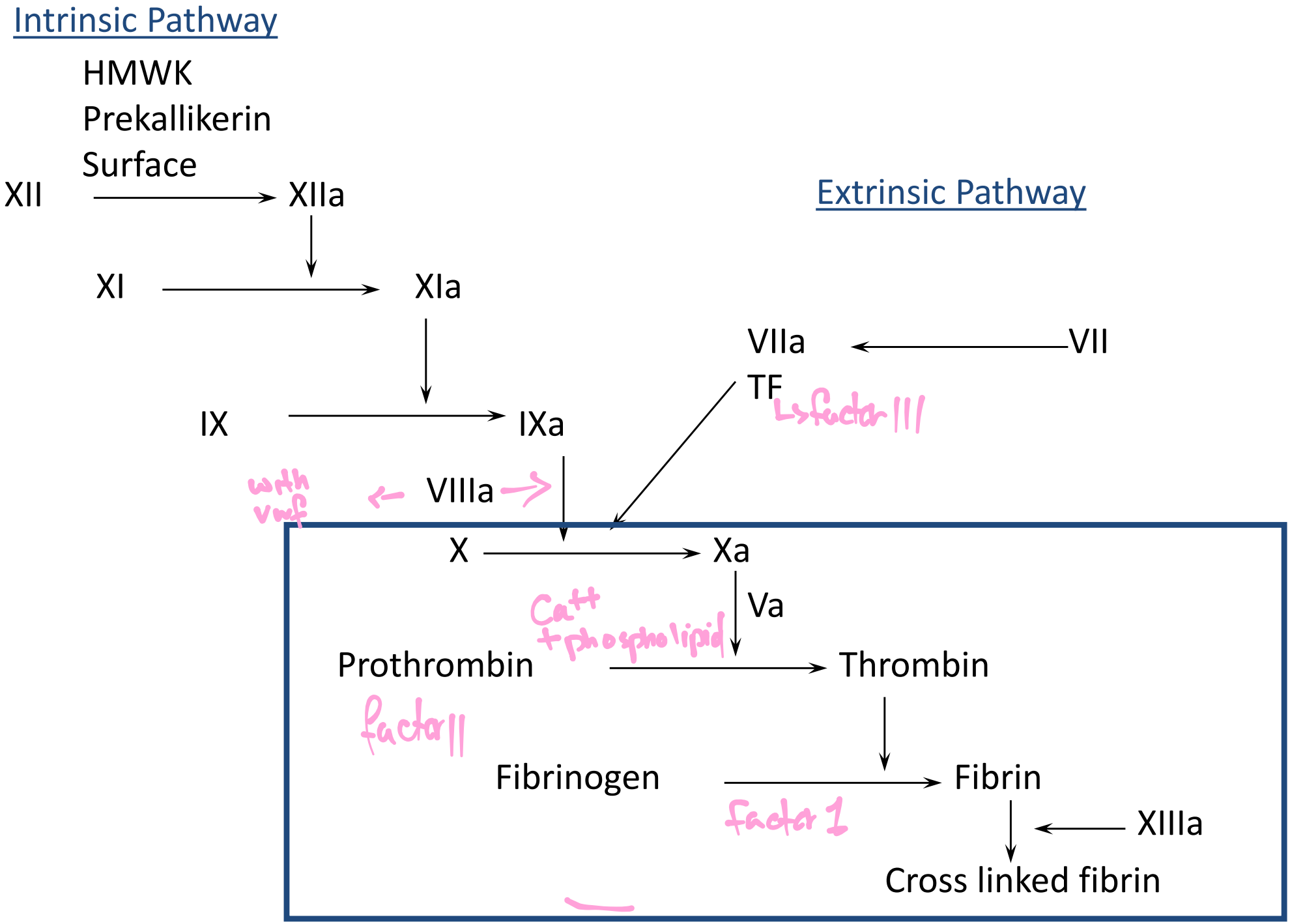


The intrinsic pathway starts with f12 (hageman factor) —>HMWK (from exposed collagen)
Kallikrein activates factor 12 ->11->9->8
8+9 activates 10

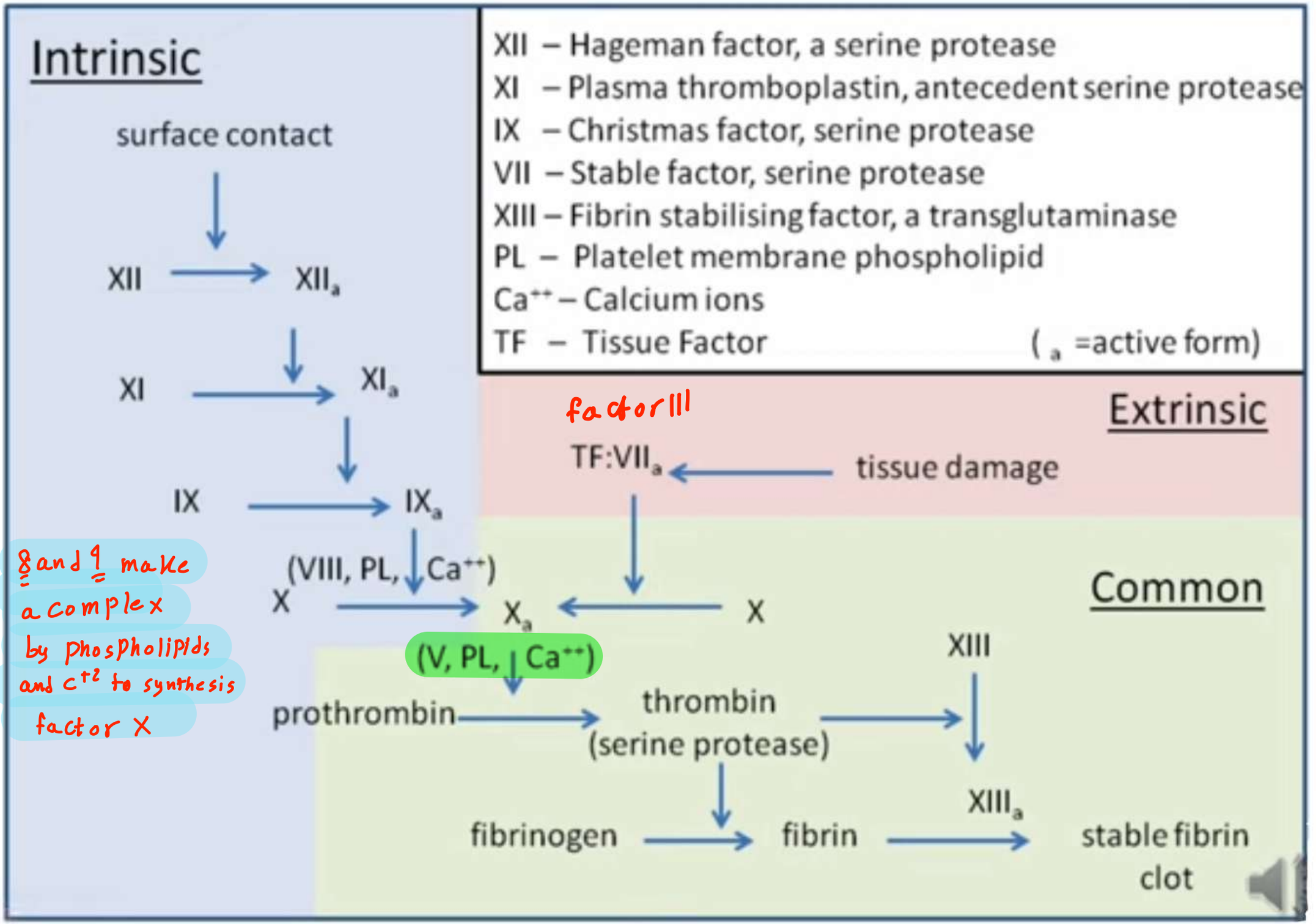
10+Ca+phospholipids +activated factor Va converts prothrombin->thrombin this coverts fibrinogen to fibrin and the factor 13 stabilise fibrin

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

III


Intrinsic Pathway
HMWK
Prekallikerin
Surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
with vwf
Extrinsic Pathway
VIIa
VII
TF
factor III
X
Xa
Va
Ca++ +phospholipid
Prothrombin
factor II
Thrombin
Fibrinogen
factor 1
Fibrin
XIIIa
Cross linked fibrin

The three pathways that makeup the classical blood coagulation pathway



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.

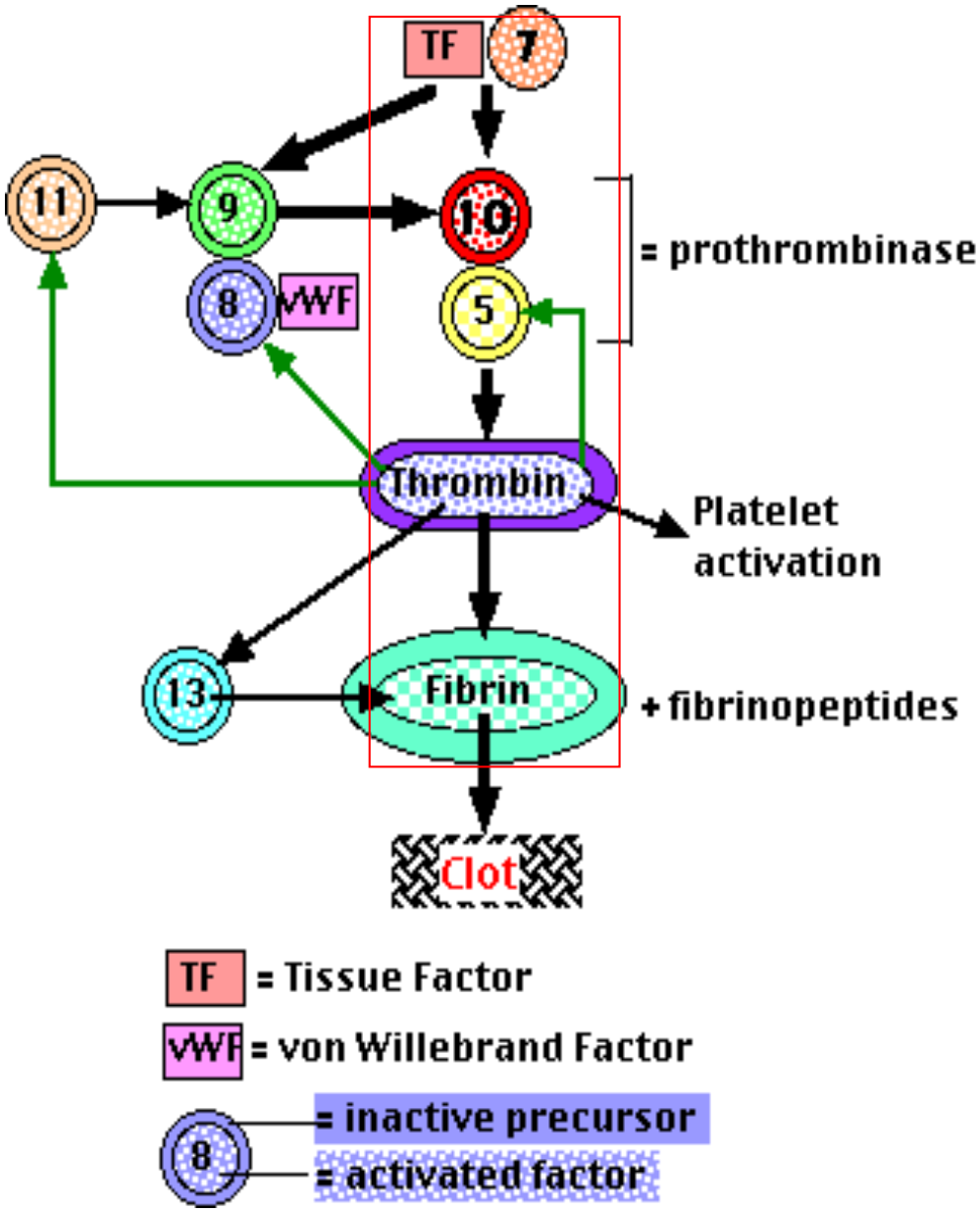
1972

- This reaction requires vitamin K as a cofactor

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

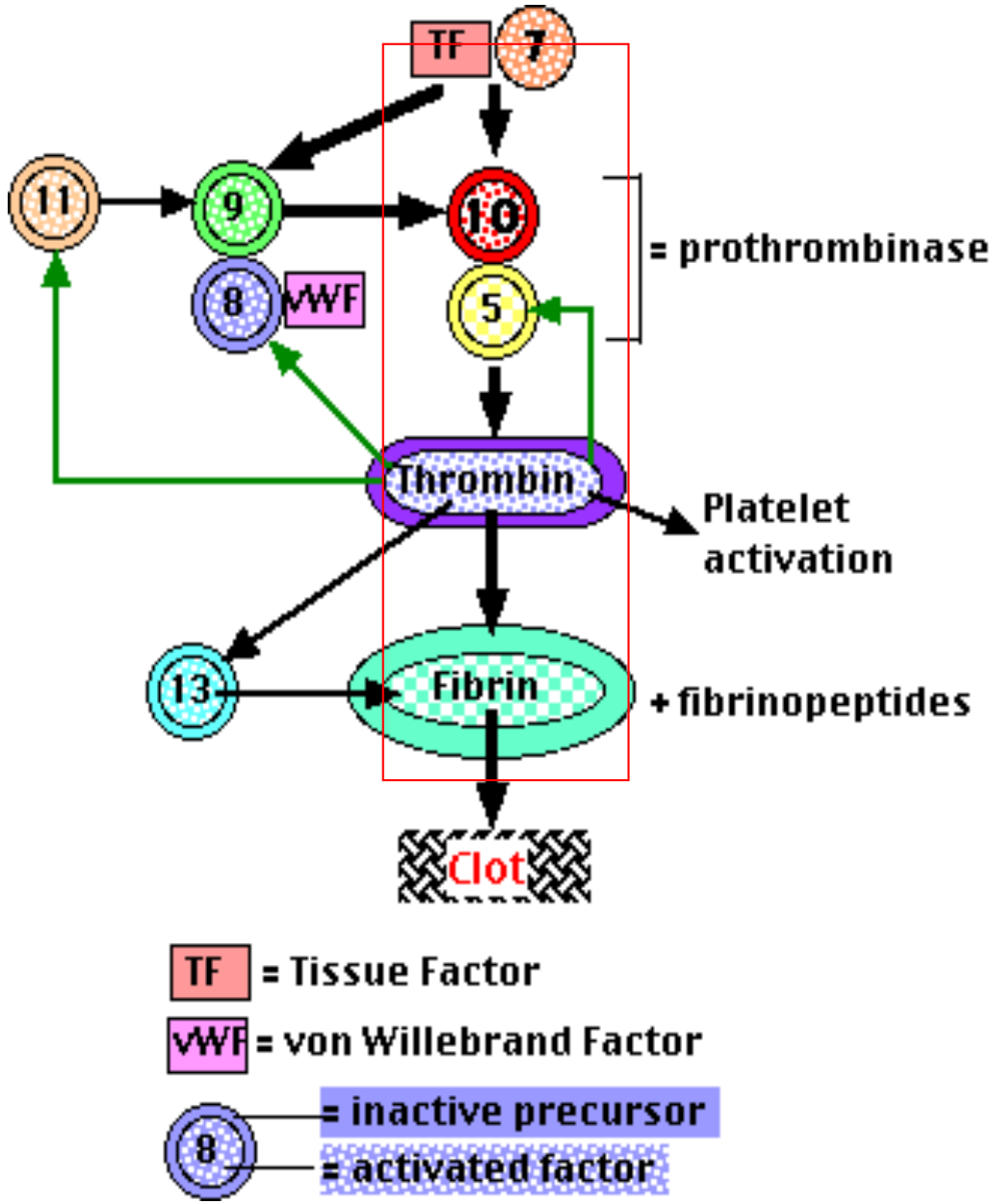
2. Factor 10 binds and activates Factor 5 (prothrombinase) converting prothrombin (also known as Factor II) to thrombin



Coagulation cascade

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

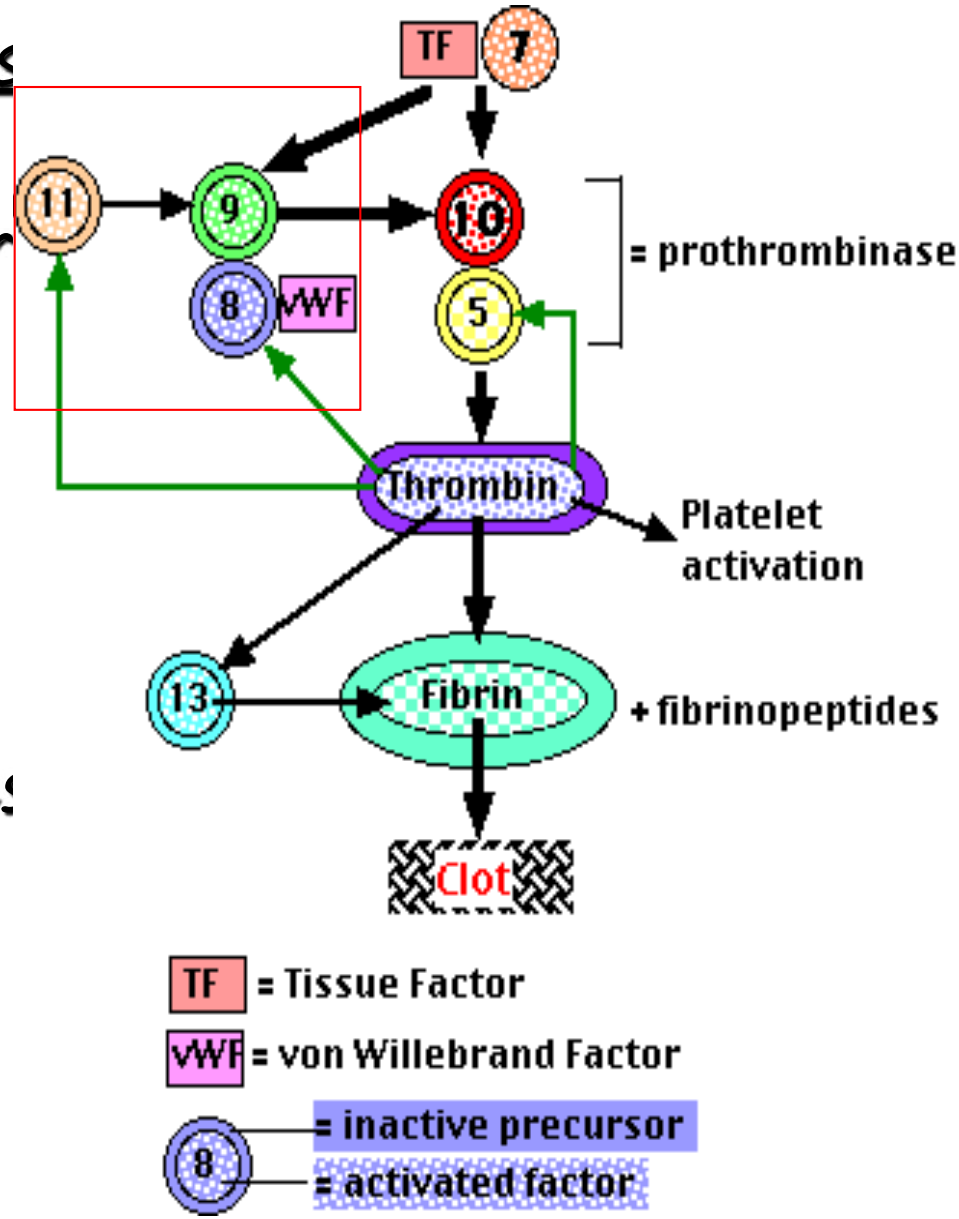
4. Factor 13 forms covalent bonds between the soluble fibrin molecules converting them into an insoluble meshwork — the clot.



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

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

الدكتورة حكت الجداول مش مطلوبة اللي مطلوب هو الشرح

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):**

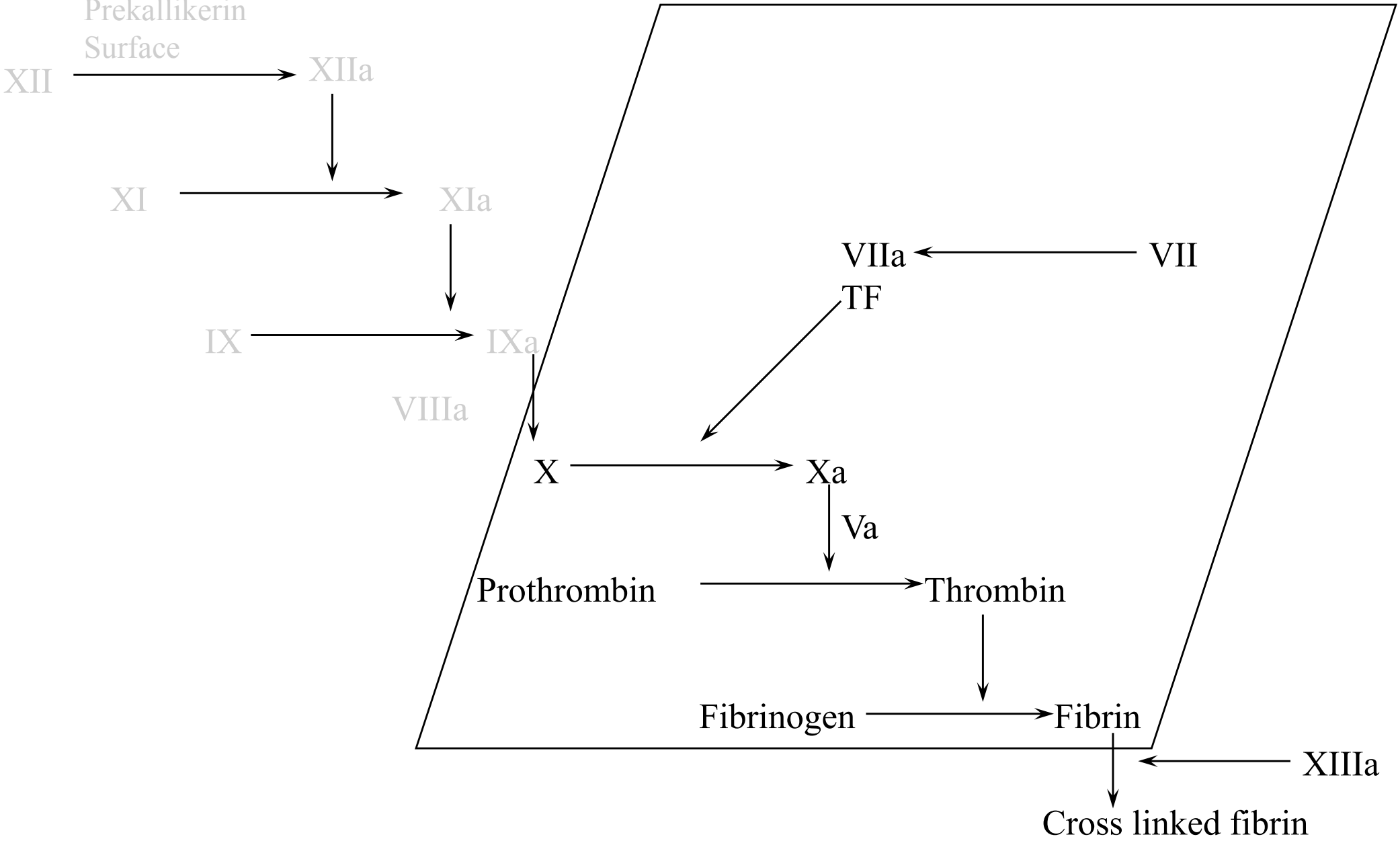
- Screens for the activity of the proteins in the **extrinsic** pathway (factors **VII**, X, II, V, and fibrinogen).
- The PT is performed by adding phospholipids and tissue factor to a patient's citrated plasma (sodium citrate chelates calcium and prevents spontaneous clotting), followed by calcium,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

PT checks the extrinsic ال نشوف متى يتكون fibrin
لو في مشكلة بال extrinsic الجسم يحول intrinsic ويزيد الوقت

First they add TF مصمم
clot ال بعدها يحسبوا متى تكونت

PTT checks the intrinsic
longer

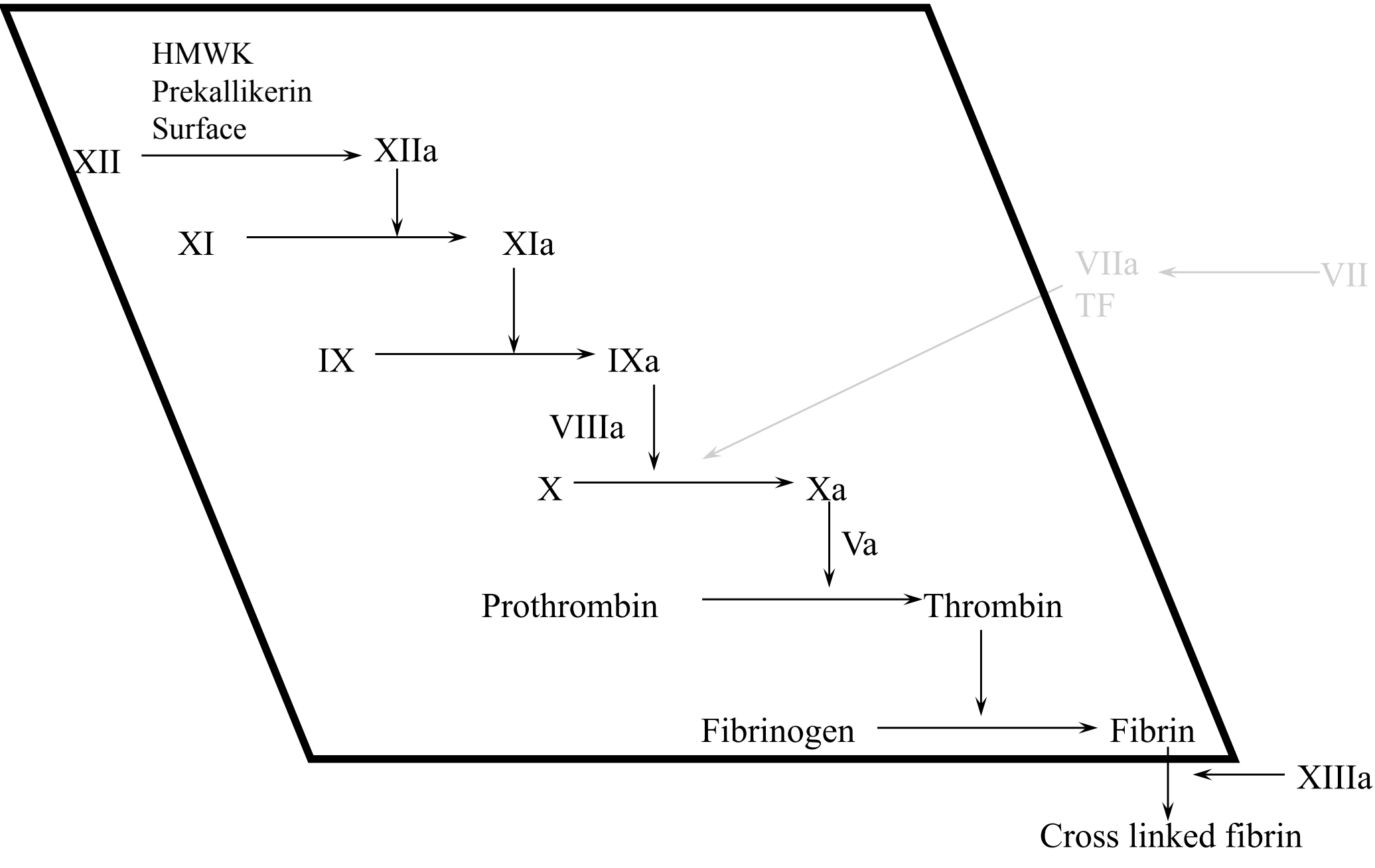
Prothrombin Time(PT)



- **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.

fibrinogen 207 → abnormal

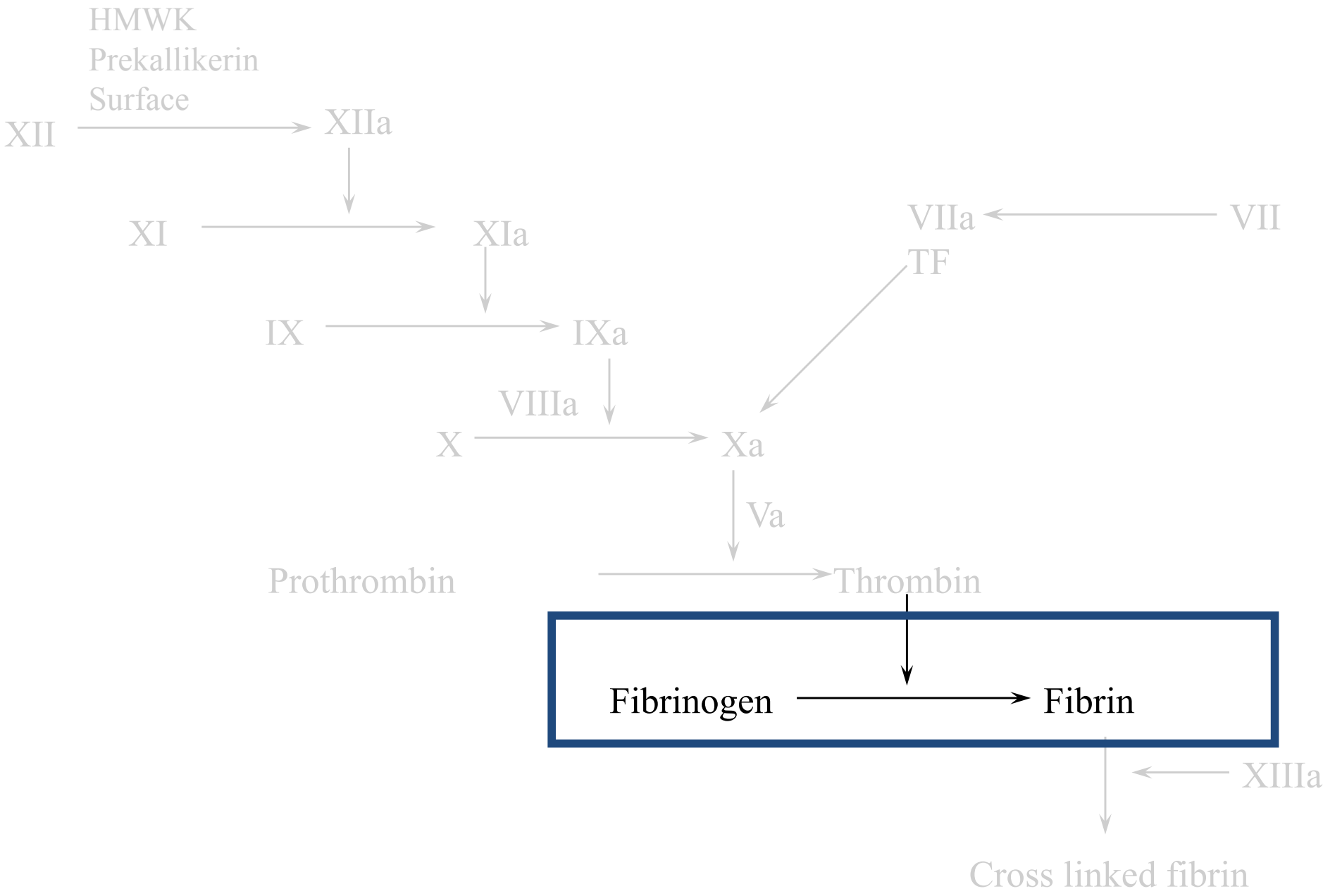
Q

سؤال: ليش بسحب دم من المريض و نحطه بـ (Tube) بصير له (coagulation) ؟؟؟

- لو سحبنا دم و حطيناه بـ (tube) أول منطه بصير (wet) تبلل فعار ال (Negative charge tube)

فسوا (Activation) لل (hageman factor-XII) فبمشي بـ (intrinsic Pathway) و بصير التخثر

Thrombin Time



Vitamin K : is a cofactor that is needed to synthesis of coagulating factors

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: -> cofactor for C

- 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):

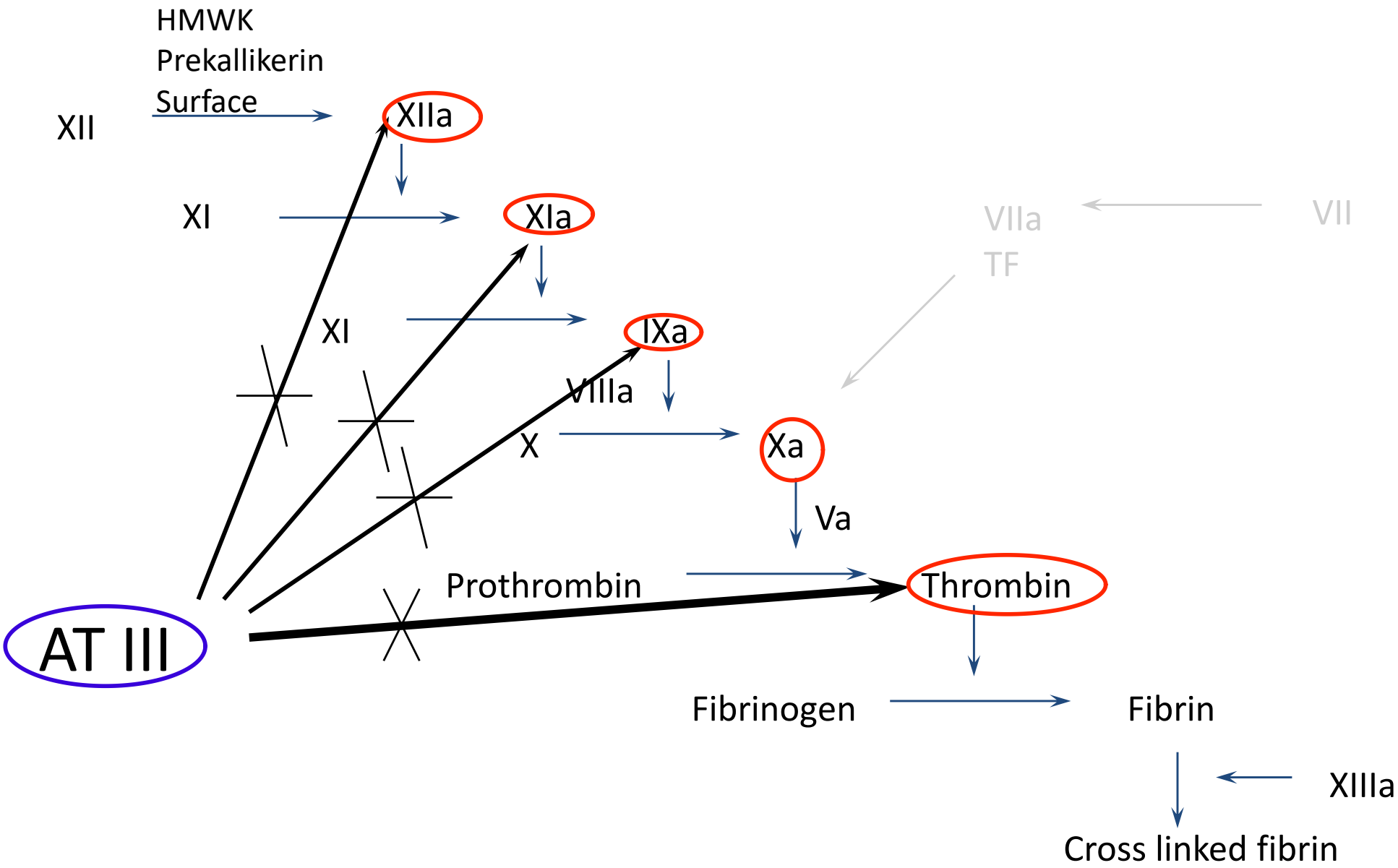
- **Inactivates factor Xa and tissue factor–factor VIIa complexes**

4- Plasmin

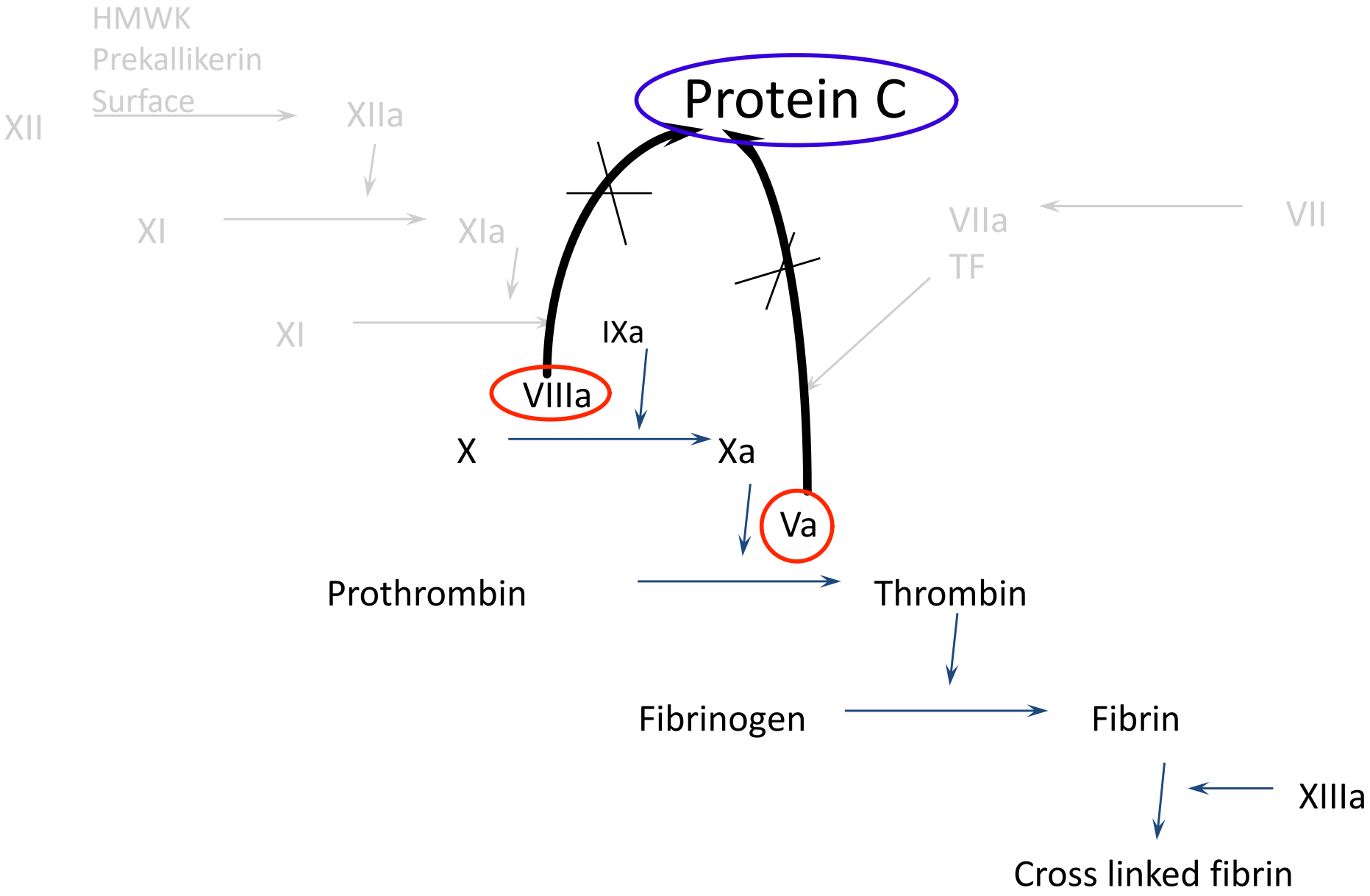
-> fibrinolysis

hemophelia -> (factor VIII, IX) -> Bleeding
↑ B
-> PTT ↓

Antithrombin III



Protein C


HMWK
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Surface
XII
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X
Xa
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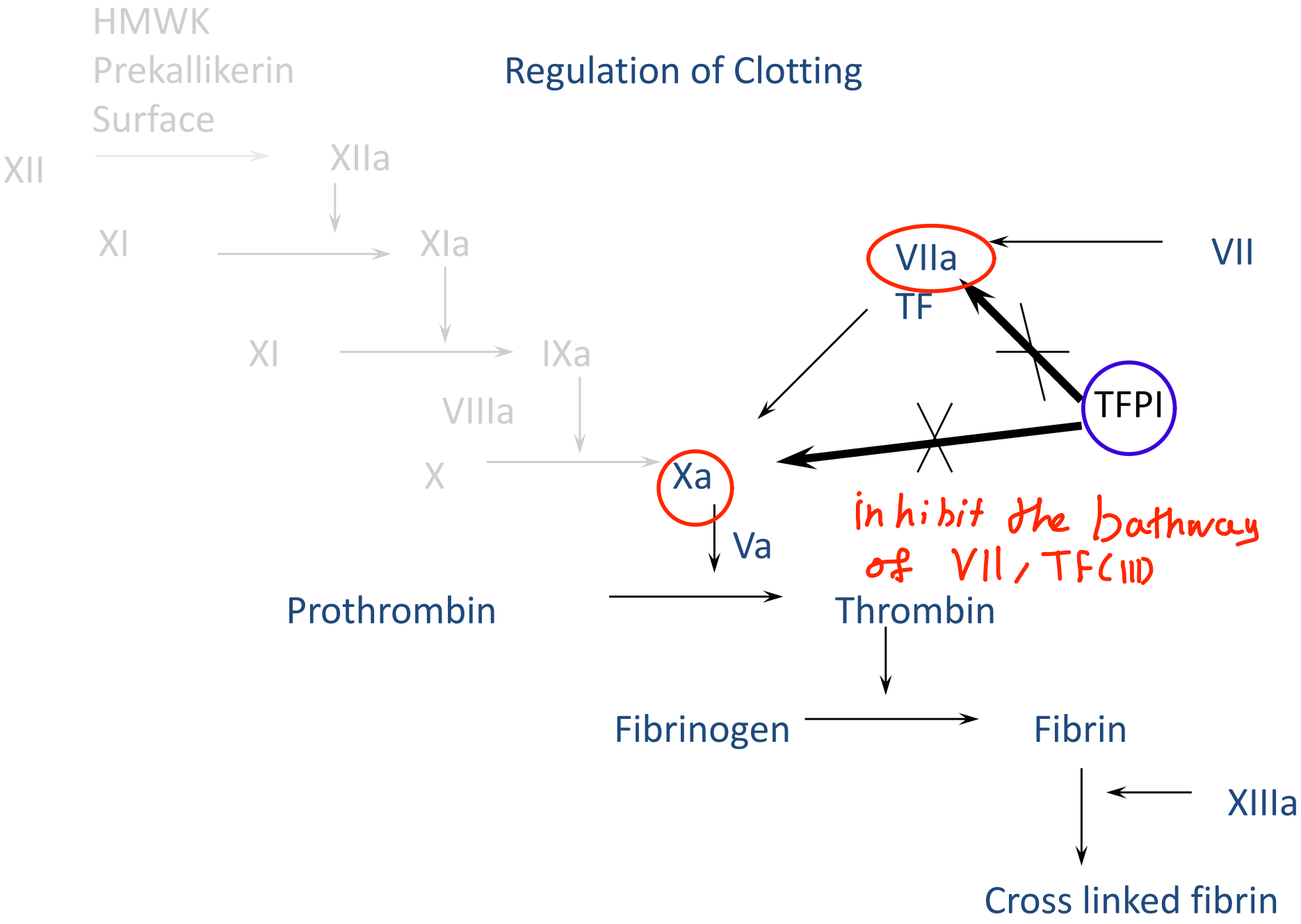
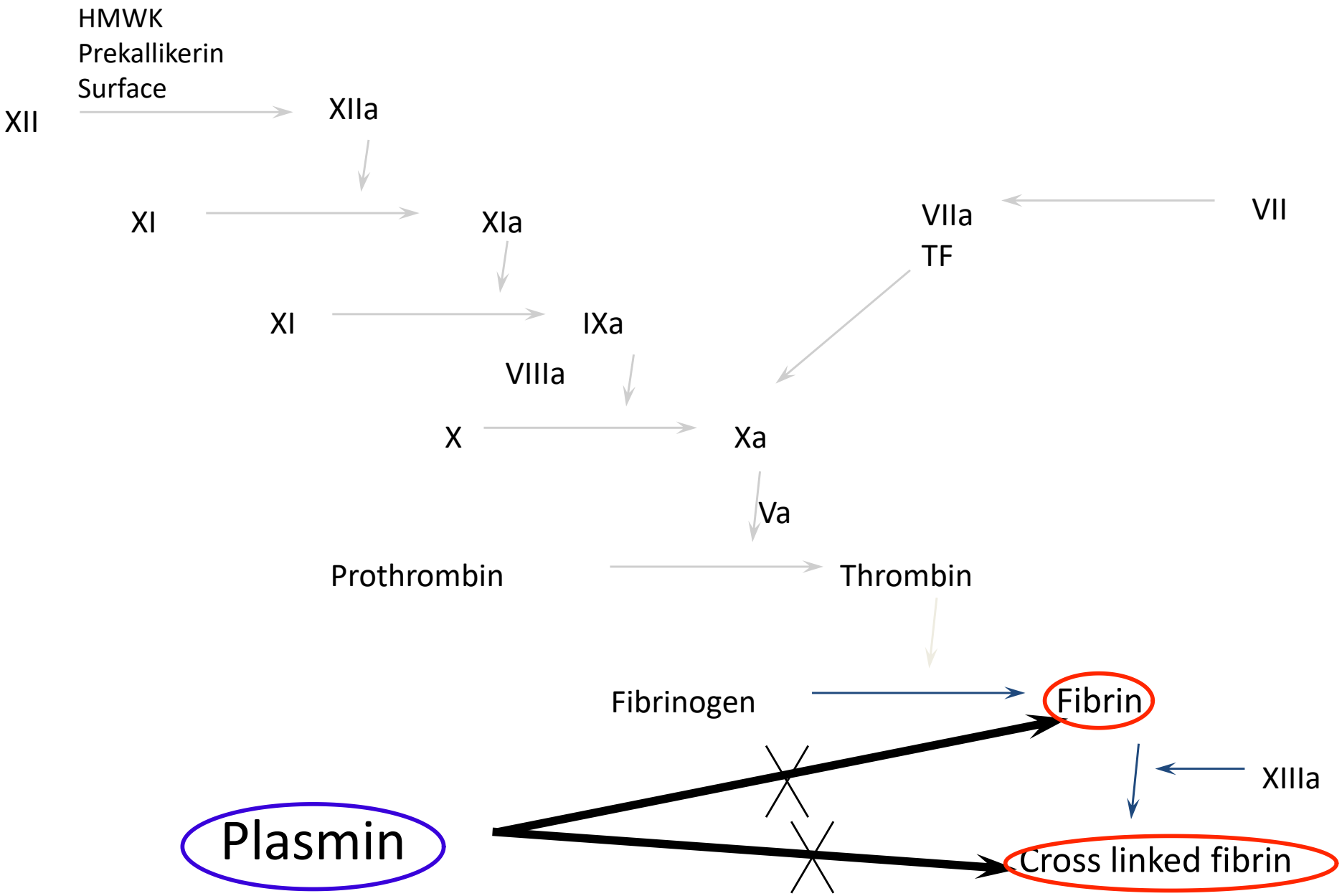
Protein C
VIIa
TF
VII
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIIIa
Cross linked fibrin

Regulation of Clotting



Plasmin


HMWK
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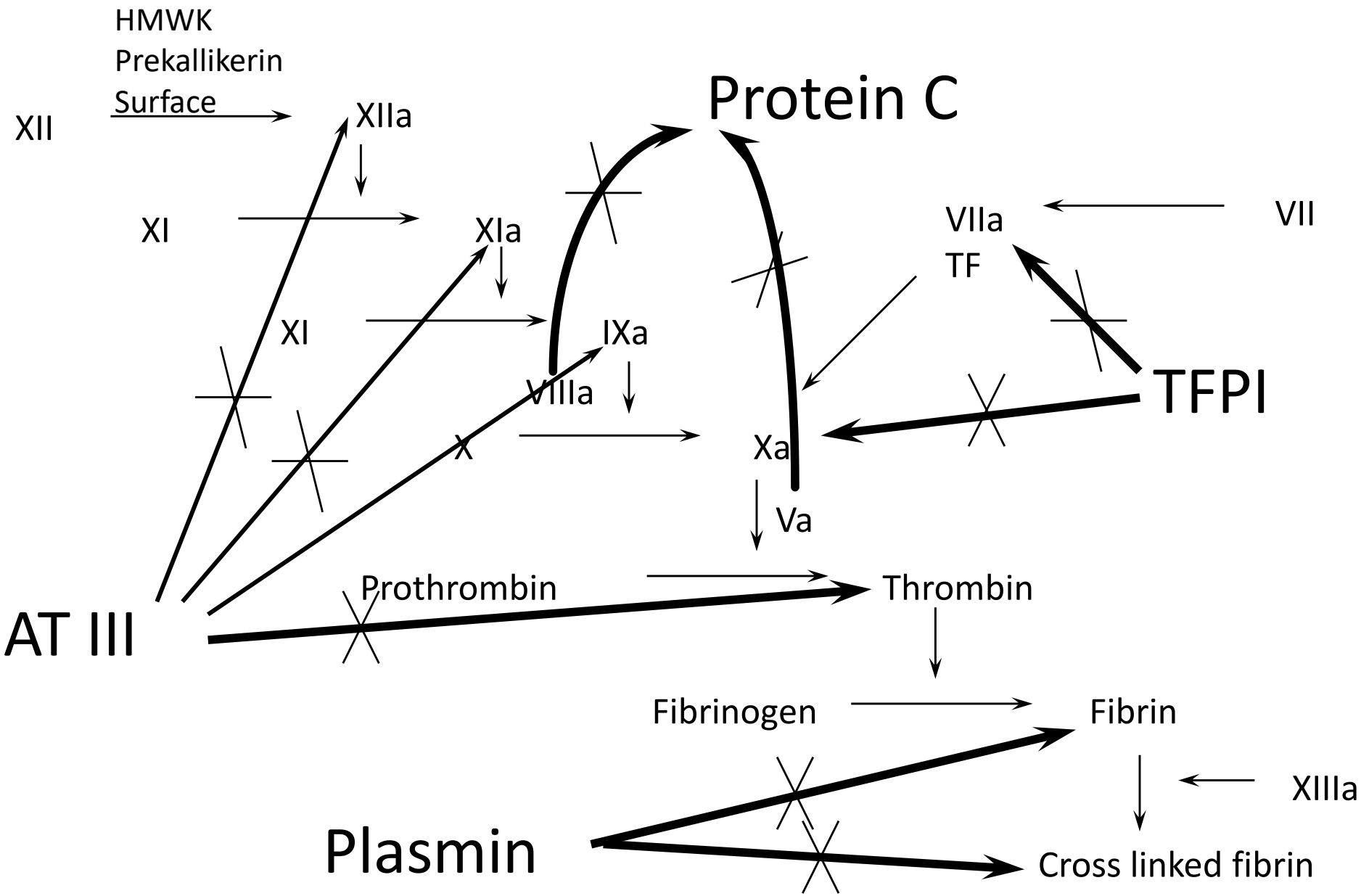
Regulation of Clotting



هاد شرح زيادة بسهل الفهم

بدي اشرح و تبعوا الكلام مع الصور سوا .. بلشوا بالصورة اللي تحت لانها ابسط و أوضح و لما نخلص شوفوا صورة السلايد بتصير مفهومة ..

بالأول في عندي طريقين ممكن يوصلوني لهدفي ، و همه :

Extrinsic pathway and intrinsic pathway

و هدول بالاخر رح يتلاقوا مع بعض بال Common pathway عند Factor X هسا بنشوف كيف ..

Extrinsic pathway

هيي نفس الحكي اللي شرحناه قبل شوي .. انو ال Factor III بعمل تنشيط لل Factor VII

$$VII \xrightarrow{\text{Factor III}} VIIa$$

بيجي ال VIIa اللي هو ال activated VII (اي واحد جنبه a يعني خلص هاد متنشط و جاهز للشغل) بيعمل activation of factor X عشان يدخل ال Common pathway

$$X \xrightarrow{\text{Factor VIIa}} Xa$$

كل واحد نشّط اللي وراه .. لهيك بالبدايه حكينا بتعريف العملية انها series (رقم 3 نشّط 7 .. و 7 نشّط 10) لهون تمام؟ نيجي للثانيه ..

Intrinsic Pathway

أول شي بتبلش ب Hagman factor (factor XII) .. هاد حكينا عنو بتشابتر ال inflammation انو عبارة عن بروتين بتم صناعته بالكبد و بكون موجود بالدم ب inactive form و بتحول الى active form عشان يشارك ب 4 systems .. اذا متذكرين كان بينهم Clotting system .. طيب مين اللي بنشطه اصلا؟ HMWK

HMWK = high molecular weight kininogen

تذكرناه؟ هسا بدنا نشوف دوره هون .. حكينا هو بيلش .. طيب شو بيعمل؟ بنشّط Factor XI (هو 12 و نشطلي 11)

$$XI \xrightarrow{\text{Factor XII}} XIa$$

بيجي ال XIa بنشط IX (بالتالي بكون 12 نشط 11 .. و 11 نشط 9)

$$IX \xrightarrow{\text{Factor XI}} IXa$$

بس IXa ما بقدر استفيد منو لحالو .. لازم يكون معه صاحبه .. اللي هو Factor VIII
(يعني 9 بدو 8 معه) .. من وين نجيبه هاد؟ بصيرلو activation عن طريق ال thrombin
تمام؟
بيجوا هدول الاصحاب بدهم يعملوا activation of factor X عشان يدخلوا ع ال common pathway
بس ما بقدروا يدخلوا يشتغلوا بدون ايونات Ca^{+2} .. و لازم كمان ال surface يكون من phospholipid

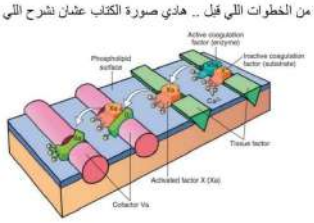
$$X \xrightarrow{\text{IXa, VIII, } Ca^{+2}\text{, Phospholipid surface}} Xa$$

برضو نرجع نشبك .. (12 بنشط 11 .. و 11 بنشط 9 .. و 9 بدها 8 عشان ينشطوا 10)
هيك تمام؟ وصلنا بالطريقين لرقم 10 .. هسا التكملة وحده
بس قبل ما نطلع من هون بدي ارجع شوي احكي عن Hagman factor (factor XII)
بعد ما يتنشط حكينا الو كثير شغل و شرحنا شغله هون .. في الو كمان شغلة ثانيه بدنا نعرفها
انو بحوّل ال Prekallikrein الى kallikrein
و هاد عباره عن انزيم بكسّر ال Peptide bonds بالبروتينات .. مش مطلوب هاد الاشي يعني بس
اعرفوا انو بينعملله activation

نرجع نكمل هسا ..

Common Pathway

حكينا انها نتجت من الخطوات اللي قبل .. هادي صورة الكتاب عشان نشرح اللي بصير



نتذكر نهاية الطريقين اللي قبل

$$\text{Extrinsic pathway: } X \xrightarrow{\text{VIIa}} Xa$$

$$\text{Intrinsic pathway: } X \xrightarrow{\text{IXa, VIII, } Ca^{+2}\text{, phospholipid surface}} Xa$$

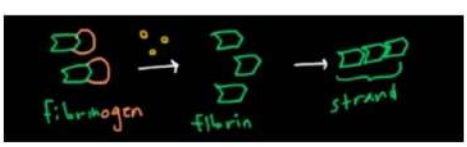
طيب بعد ما عملنا activation of factor X شو بصير؟
ال Xa بحكي انا كمان ما بروح لحالي .. بدو معه Factor V (يعني 5 و 10 مع بعض)
و برضو هدول بلزمهم ايونات Ca^{+2} و Phospholipid surface
بيجوا هدول المجموعه بدهم يحولوا ال prothrombin الى thrombin
بالتالي وصلت للي بدي ياه

$$\text{Fibrinogen} \xrightarrow{\text{thrombin}} \text{Fibrin}$$

هيك خلص ..

ضل اخر شي.. لما ال fibrin بدو يروح على منطقة النزف ما بروح هيك قطع .. بجمعوا حالهم و
بعملوا مركب بنسميه Cross-linked fibrin .. مين بخليهم يعملوا هيك؟ Factor XIIIa (يعني 13)

$$XIII \xrightarrow{Ca^{+2}} XIIIa$$



اللَّهُمَّ صَلِّ وَسَلِّمْ وَبَارِكْ

عَلَى نَبِيِّنَا مُحَمَّدٍ ﷺ