Doctor.021

no. 6

HLS

BIOCHEMISTRY

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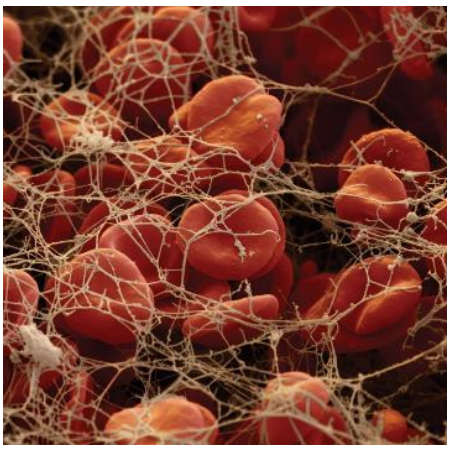
Blood Coagulation

Slides will be in black, doctor's notes in pink.

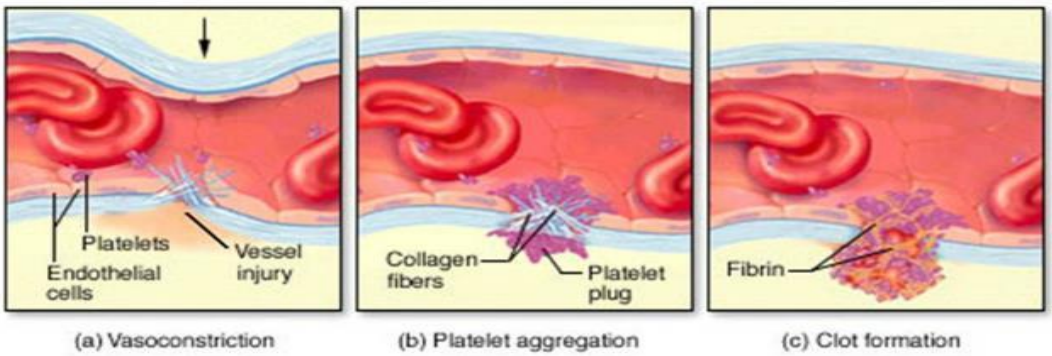
➢ WHAT IS BLOOD COAGULATION (CLOTTING)?



It is an orchestrated, biochemical process (group of cells and proteins work together to regulate blood coagulation) that is initiated as a result of vascular injury (internal or external) where a small area blood of surrounding injury changes from liquid to gel, forming a clot made of fibrin (to stop blood flow), which results in hemostasis (the cessation of blood loss) followed by clot dissolution and repair.

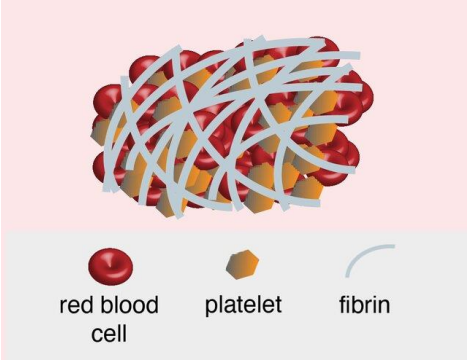
➢ STEPS OF HEMOSTASIS AND THROMBOSIS

- **Vascular constriction limiting blood flow to the area of injury**
- **Activation then aggregation of platelets at the site of injury, forming a loose platelet plug (gel)**
- **Formation of a fibrin mesh to entrap the plug**
- **Dissolution of the clot in order for normal blood flow to resume following tissue repair**



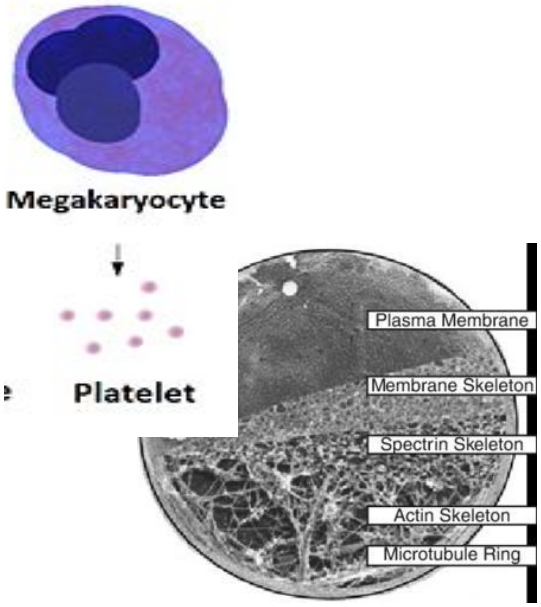
➢ COMPOSITION OF CLOT

The main components of clot are RBCs, platelets, and fibrin.
Fibrin is a fibre that surrounds cells and molecules. Proportion of RBCs and platelets changes according to the type of the clot and injury.



➢ PLATELETS ARE A MAJOR PLAYER

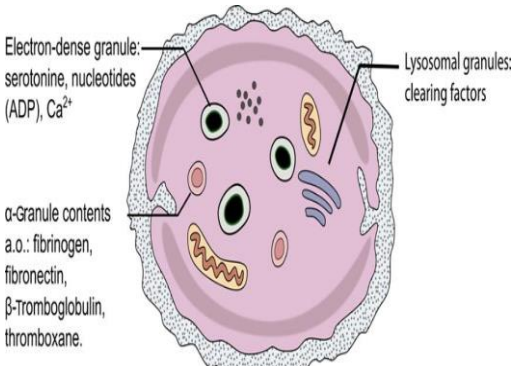
- Small anuclear cell fragments produced from the megakaryocytes.
- Platelets have numerous kinds of surface receptors.
- Platelets also have actin filaments and myosin, which change the shape of the platelet upon activation (which allows aggregation to form platelet plug).
- They also have three types of granules that store substances that are released upon platelet activation.



➢ THE GARNULES

They are three types:

- Electron-dense granules, they contain signaling molecules: (calcium ions, ADP, ATP, serotonin)
- α-granule (a heparin antagonist, platelet-derived growth factor, fibrinogen (makes fibrin), von Willebrand factor (vWF), clotting factors)
- Lysosomal granules (hydrolytic enzymes) these enzymes are responsible for clot clearing.



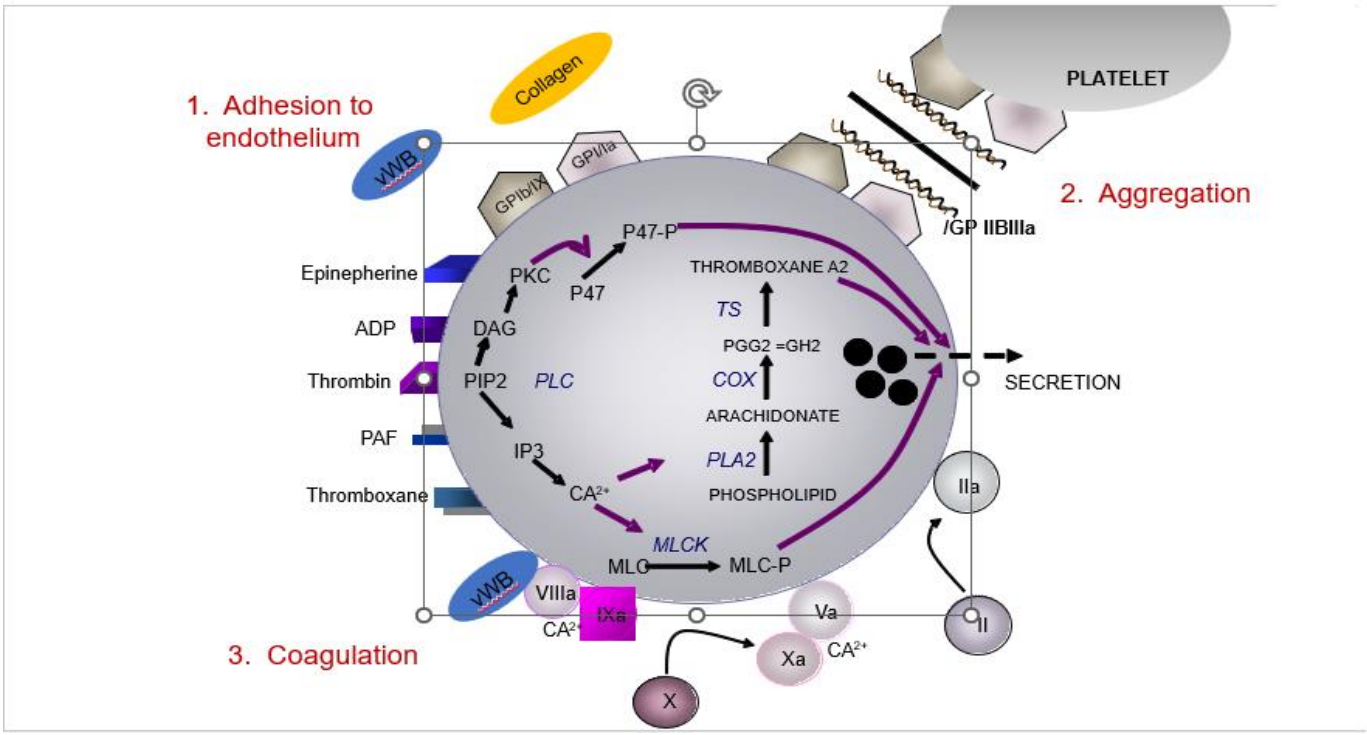
We said before that platelets have surface receptors; each is specific for a certain ligand. For example, there is a receptor for ADP, another for thrombin and one for thromboxane. In addition, there are glycoproteins on cell surface, they make interactions with collagen.

Collagen is always hidden except injuries, so in injuries, collagen becomes visible and binds to glycoproteins.

There are another glycoproteins, their function is making platelet-platelet interaction for aggregation.

We will talk about vwf later.

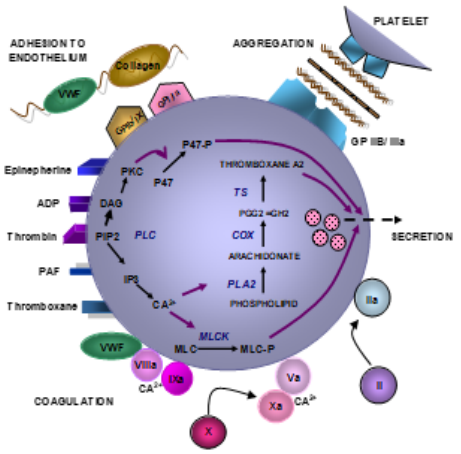
- So, they are 3 steps:
  1. Platelets adhere to endothelial cell surface through vwf and interaction with exposed collagen.
  2. Platelets aggregation to make platelet plug.
  3. Coagulation.



➢ ADHESION

- The endothelial von Willebrand factor (vWF) protein and exposed collagen bind to the platelet glycoproteins (GP).
- Some platelets release substances from the granules:
  - ADP
  - Serotonin
  - Factor V
  - ATP
  - Calcium
  - Fibrinogen
  - vWF
  - Thrombin
  - Thromoxane

Bind to receptors



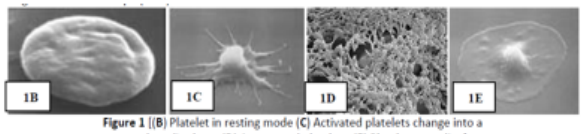


Figure 1 [(B) Platelet in resting mode (C) Activated platelets change into a pseudopodia shape (D) Aggregated platelets (E) Platelet spreading]

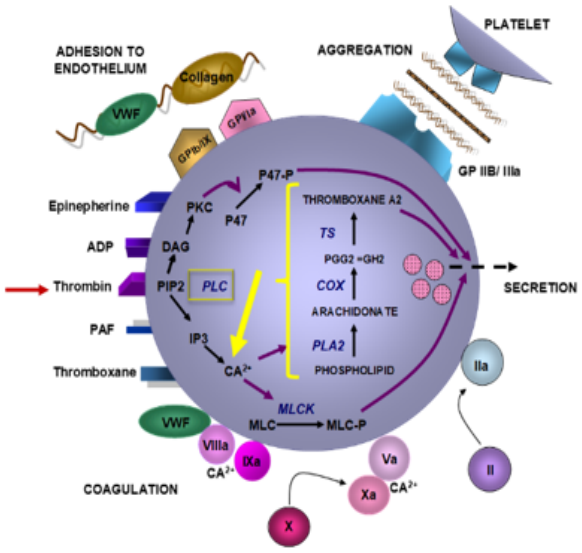
- Platelets also change their shape allowing for more platelet-platelet interaction and aggregation.

In injuries, platelets make interactions with exposed collagen and vwf, this leads to release of different substances from platelets.

Notice the small picture on right, the morphology of platelets is changing but what are the inducers of platelet morphology?

➢ THROMBIN RECEPTOR

- Thrombin receptor activates a G protein that activates phospholipase C-β (PLC-β).
- PLC-β hydrolyzes phosphatidylinositol-4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (DAG).
- IP3 induces the release of intracellular Ca^{2+} stores, and DAG activates protein kinase C (PKC).
- Ca^{2+} triggers the release of arachidonate from membrane phospholipids by phospholipase A2.
- Arachidonate is converted by cyclooxygenase to prostaglandins, which are then converted by thromboxane synthetase to thromboxane A2.
  - Thromboxane is as vasoconstrictor and a further inducer of PLC-β activity (and platelet aggregation).
  - It acts in autocrine and paracrine manners.



- *Serotonin is also a vasoconstrictor.*
- *PDGF stimulates proliferation of endothelial cells to reduce blood flow.*

❖ **Cyclooxygenase is responsible of making eicosanoids (thromboxane & prostaglandins), this enzyme is very important, so it's target of NSAID.**

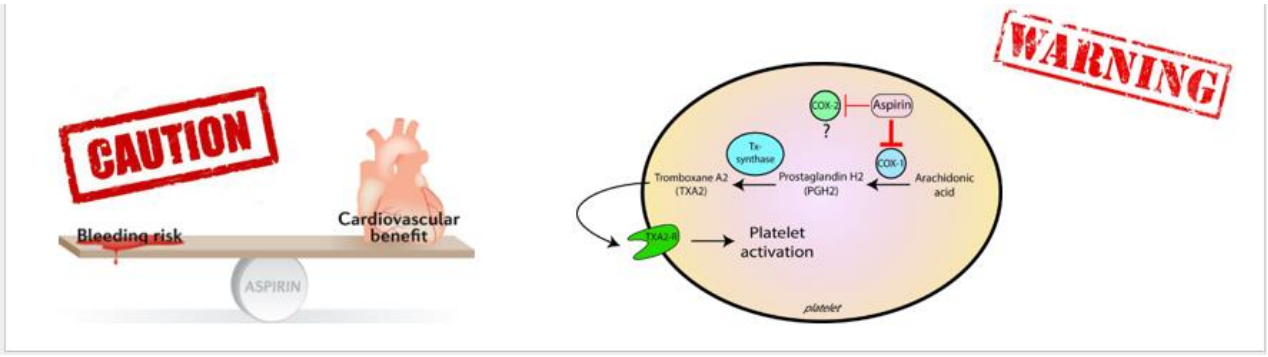
➢ NSAID

- **Non-steroidal anti-inflammatory drugs inhibit the cyclooxygenase, accounting for their anticoagulant effects.**

Remember that we have three isoenzymes of cyclooxygenase (cox1, cox2, cox3), and these cyclooxygenases are target of aspirin.

Aspirin also inhibits production of endothelial prostacyclin (since they are vasodilators, they are responsible of reducing inflammatory effects and they inhibits platelets aggregation), but, unlike platelets, these endothelial cells regenerate cyclooxygenase within a few hours. Thus, the overall balance between TxA2 and PGI2 can be shifted in favor of the latter.

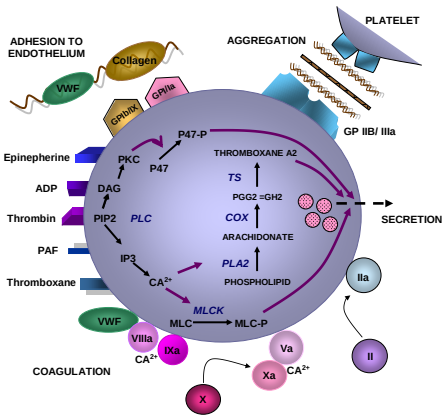
Aspirin has a high risk, since it can cause excessive bleeding specially in elderly, so the dose of aspirin must be balanced.



➢ MORE RELEASE OF GRANULAR CONTENTS

Here, we have release of calcium ions from stores, which bind to PLA2 and to a protein called MLCK which phosphorylates myosin light chain and changes the morphology of platelets by modulating the actin cytoskeleton and promotes releasing granular contents.

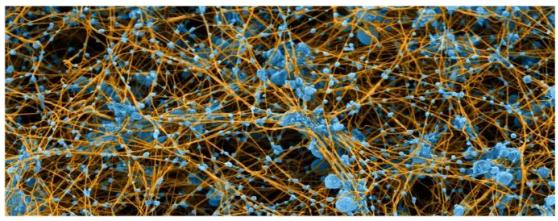
- **Ca^{2+} activates myosin light chain kinase (MLCK), which phosphorylates the light chain of myosin allowing it to interact with actin and resulting in altered platelet morphology, induced motility, and release of granules.**
- **DAG activates PKC, which phosphorylates and activates specific platelet proteins that induce the release of platelet granule contents including ADP.**



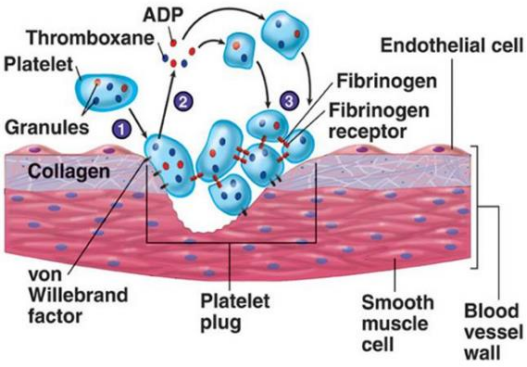
So, what is the role of ADP?

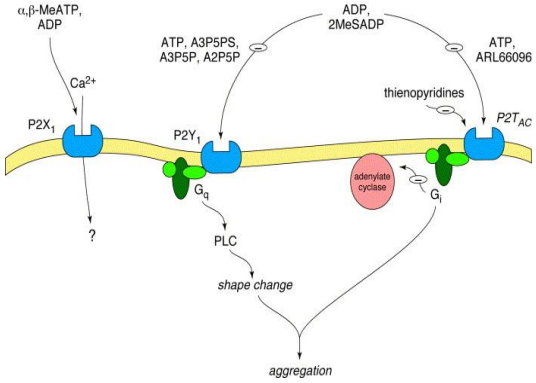
➢ ADP DRIVES THE FORMATION OF PLATELET PLUG

- **ADP is a platelet activator that binds to its receptor and modifies the platelet membrane allowing fibrinogen to adhere to platelet surface glycoproteins resulting in fibrinogen-induced platelet aggregation, called platelet plug.**



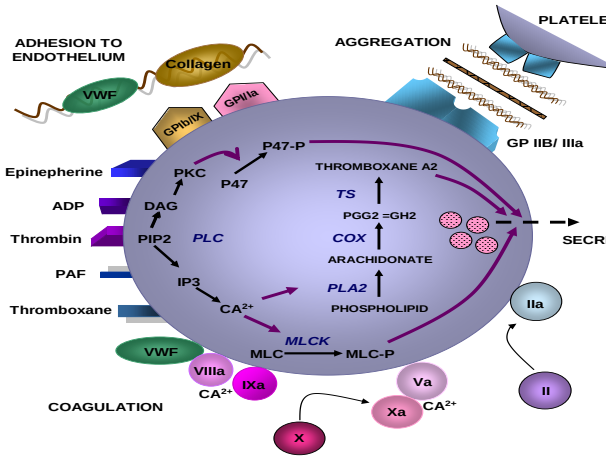
What happens is that platelets are activated, then they release substances such as ADP, ADP changes the morphology of platelets allowing them to interact with fibrinogen. So, we have now platelet-platelet interaction mediated by fibrinogen.





➢ ROLE OF PLATELET CELL SURFACE

- **The accumulated platelet plug provides an important surface on which coagulation reactions occur.**



BIOCHEMISTRY OF COAGULATION

➢ COMPONENTS OF COAGULATION

- **An organizing surface (platelets)**
- **Proteolytic zymogens "inactive enzymes undergo proteolytic activation" (prekallikrein, prothrombin, and factors VII, IX, X, XI, XII, and XIII)**
  - **These are mainly serine proproteases released from hepatocytes.**
  - **The subscript "a" designates the activated form of a factor.**
    - e.g., "XIII" is versus "XIIIa activated"
- **Anti-coagulants (protein C, protein S)**
- **Non-enzymatic protein cofactors (factors VIII, V, and tissue factor)**
- **Calcium ions**
- **Vitamin K important for coagulation**
- **Fibrinogen**

Table 3: illustrates the engagement and detailed explanation of coagulation factors, that aid in the blood coagulation cascade

Factor	Name	Source	Pathway	Description	Function
I	Fib	Liver	Common	Plasma glycoprotein; Molecular Weight (MW)= 340 kilodaltons (kDa)	Adhesive protein which aids in fibrin clot formation.
II	Prothrombin	Liver	Common	Vitamin K-dependent serine protease; MW= 72 kDa	Presence in the activated form and the main enzyme of coagulation
III	Tissue factor	Secrete by the damaged cells and platelets	Extrinsic and Intrinsic	Known as thromboplastin; MW= 37 kDa	Lipoprotein initiator of the extrinsic pathway
IV	Calcium ions	Bone and gut	Entire process	Required for coagulation factors to bind to phospholipid (formerly known as factor IV)	Metal cation which is important in coagulation mechanisms
V	Proaccererin / Labile factor	Liver and platelets	Intrinsic and extrinsic	MW = 330 kDa	Cofactor for the activation of prothrombin to thrombin (prothrombinase complex)
VII	Proconvertin (stable factor)	Liver	Extrinsic	MW = 50 kDa; vitamin K-dependent serine protease	With tissue factor, initiates extrinsic pathway (Factor IX and X)
VIII	Antihemophilic factor A (cofactor)	Platelets and endothelium	Intrinsic	MW = 330 kDa	Cofactor for intrinsic activation of factor X (which it forms tenase complex)
IX	Christmas factor / Antihemophilic factor B (plasma thromboplastin component)	Liver	Intrinsic	MW = 50 kDa; vitamin K-dependent serine protease	Activated form is enzyme for intrinsic activation of factor X (forms tenase complex with factorVIII)
X	Stuart-Prower factor (enzyme)	Liver	Intrinsic and extrinsic	MW = 58.9 kDa; vitamin K-dependent serine protease	Activated form is the enzyme for final the common pathway activation of prothrombin (forms prothrombinase complex with factor V)
XI	Plasma thromboplastin antecedent	Liver	Intrinsic	MW = 160 kDa; serine protease	Activates intrinsic activator of factor IX
XII	Hageman factor	Liver	Intrinsic; (activates plasmin)	MW = 80 kDa; serine protease	Initiates activated partial thromboplastin time (aPTT) based intrinsic pathway; Activates factor XI, VII and prekallikrein
XIII	Fibrin stabilizing factor	Liver	Retards fibrinolysis	MW = 320 kDa; Crosslinks fibrin	Transamidase which cross-links fibrin clot

Molecular components of coagulation

Notes:

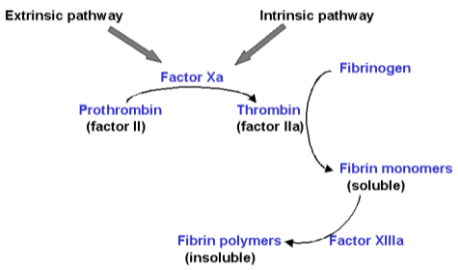
1. Names and symbols
2. Pathway
3. Sources
4. Functions
5. Do not worry about MW

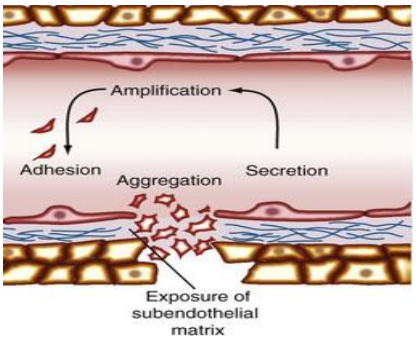
✓ **Notice that liver is the main source of these factors, with some exceptions. You need to know the source, pathway, and function of each factor.**

➢ THE TWO PATHWAYS

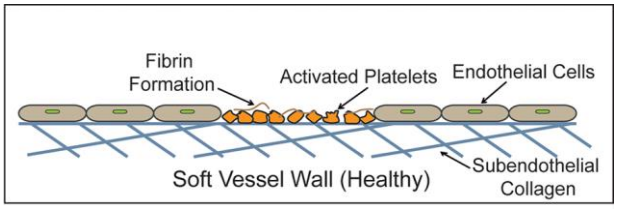
There are two pathways controlling coagulation, intrinsic & extrinsic pathways, according to the type of damage (internal or external).

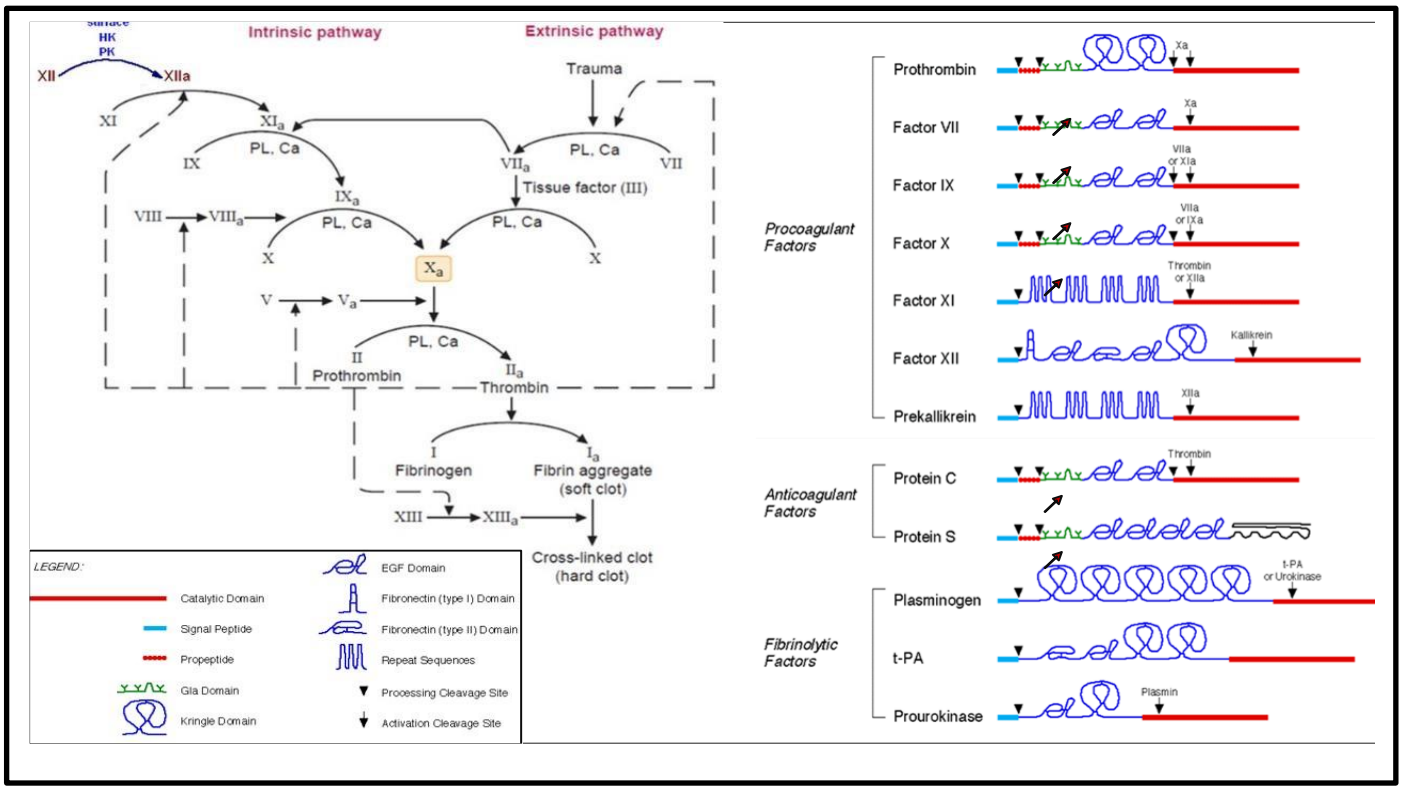
However, there is a connection between the two pathways.





- **The intrinsic pathway is initiated when subendothelial surface (i.e., collagen) is exposed.**
- **The extrinsic pathway is initiated in response to tissue injury.**
  - Tissue factor (TF) protein is released from damaged cells.
- **However, the two pathways converge on a common pathway.**



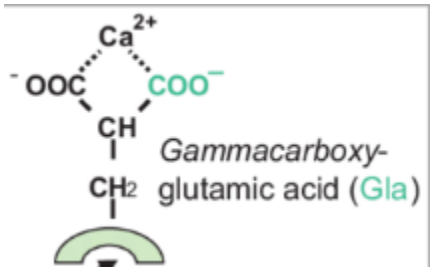


- Notice the diagram on the pervious page, the two pathways meet on factor X (10) activation. When factor X is activated, it activates thrombin "prothrombin to thrombin".
- Thrombin transfers fibrinogen into fibrin, which aggregates forming soft clot.
- This soft clot is transferred into hard clot through covalent linkage between fibrin monomers.

Look at the representation of structure of the different domains of different factors, we will concentrate on glutamate domain (the one in green).

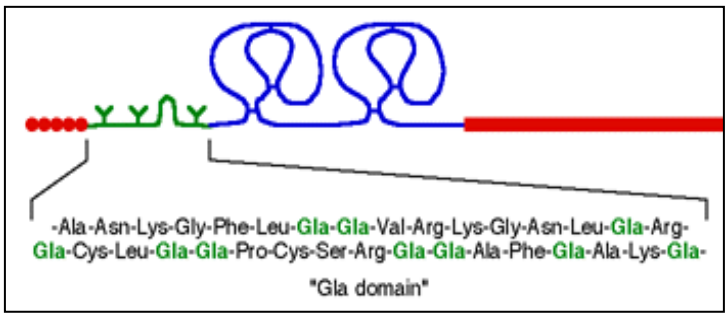
GLA DOMAIN

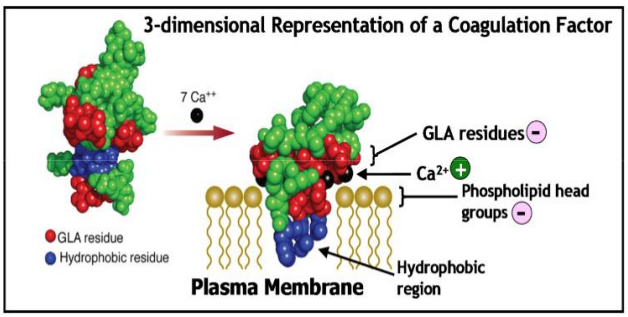
Gla domain undergoes carboxylation. Gla domain already has a carboxyl group, and another carboxyl group is added on its γ-carbon, forming γ-carboxyglutamate. When ca2+ ions are released from platelets, they form cross link between these two carboxyl groups. See the picture.



Ca2+ ions make interactions with phospholipids on platelets surface, because of phospholipids negative charge, and calcium ions positive charge, there will be interactions between proteins that contain glutamate and phospholipids, mediated by calcium ions.
Why? Our body do this to put factors together in order to activate each other "through compartmentalization".
Compartmentalization means to put the enzyme and it's substrate on cells surface to increase their chance to find each other.
Gla domain is found on factors IX, VII and X.

- An ER/Golgi carboxylase binds to prothrombin and factors IX, VII, and X and converts 10≥ glutamate (Glu) residues to γ-carboxyglutamate (Gla), followed by a small (10 a.a.) hydrophobic region.
- The Gla residues bind calcium ions and are necessary for the activity of these coagulation factors and formation of a coordinated complex with the charged platelet surface to localize the complex assembly and thrombin formation to the platelet surface.





Let's talk about carboxylation reaction.

➢ THE ROLE OF VIATMIN K

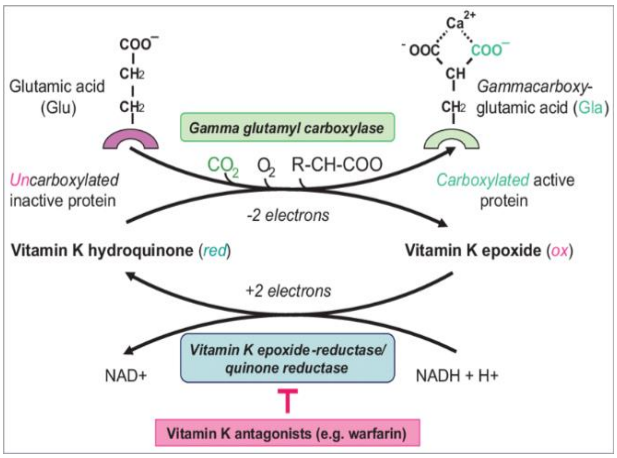
- Vitamin K participates in the conversion of Glu to γ-carboxy-Gla.
- Vitamin K becomes oxidized and must be regenerated.

This carboxylation reaction is catalyzed by a carboxylase enzyme (Gamma glutamyl carboxylase), this enzyme needs vitamin K to work. So, vitamin K is responsible of carboxylation reaction.

For vitamin K to work again, it needs regeneration through reductase enzyme.

❖ Quick summary:

1. Glutamate carboxylation catalysed by carboxylase.
2. Vitamin K is needed for the activation of the carboxylate.
3. For vitamin K to work again, it needs to be regenerated through reduction by a reductase & NADH.
4. This reductase is important since it's targeted by drugs specially warfarin.



➢ NEWBORNS & VITAMIN K DEFICIENCY

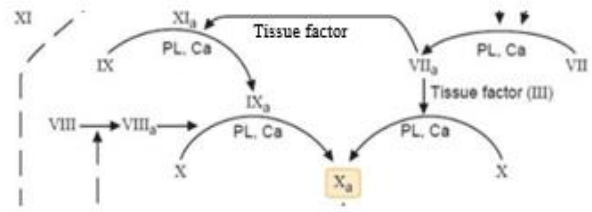
- **Newborns are at risk for early vitamin K deficiency bleeding. Why?**
  - **The placenta is a poor passage channel for fat-soluble compounds, including vitamin K.**
  - **Neonates are born with an immature liver that impairs coagulation factor synthesis and GLA modifications.**
  - **Breast milk is a poor source of vitamin K.**
  - **Intestinal flora, the main source of vitamin K, is not established yet.**

❖ **Let's talk about activation of extrinsic pathway:**

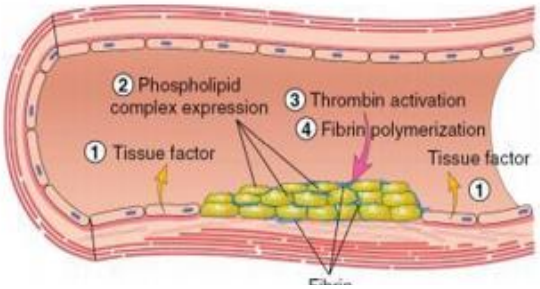
➢ TISSUE FACTOR

TF is protein released from damaged cells, it does an interaction with factor VII, which increases it's proteolytic activity (factor VII). This complex between TF & factor VII is called initiation complex.
Notice in the picture below, that TF & factor VII activate the intrinsic pathway as well.
Calcium ions & phospholipids are needed for the function of TF & VII (this happens on surface of platelets).
So, the extrinsic pathway starts from TF & VII arriving to factor X.

- **TF is an integral membrane protein that is expressed on the surface of "activated" monocytes, subendothelial cells, and other cells.**
- **It is the primary initiator of coagulation and is not exposed to blood until disruption of the vessel wall.**
- **It increases the proteolytic efficiency of VIIa.**



Exposure of tissue factor initiates the coagulation cascade.
TF/VIIa complex is the "initiation complex".



➢ INITIATION OF THE INTRINSIC PATHWAY

This in pink is doctor's explanation of the intrinsic pathway, it may help you in better understanding.

❖ **We have different components until reaching factor X (Prekallikrein, HMW kininogen, factors XII and XI) which are exposed to negatively charged activating surface (platelets).**

-factor XII has many functions:

1. It activates factor XI

2. Factor XI activates factor X

3. Factor X activates thrombin

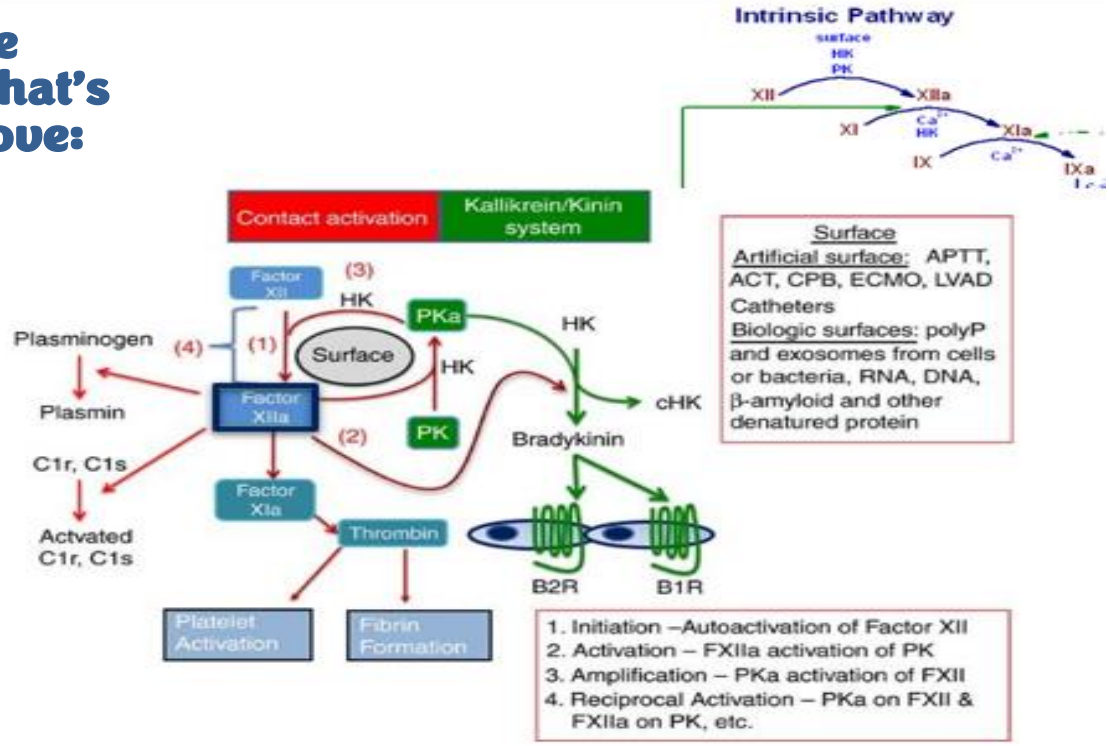
❖ **Prekallikrein is activated to kallikrein, notice that kallikrein has a positive feedback ACTIVATION on factor XII.**

❖ **Activated prekallikrein (PKa) activates HMW kininogen to bradykinin (vasodilator).**

❖ **Note: factor XII activates HMW kininogen as well.**

- **Prekallikrein, HMW kininogen, factors XII and XI are exposed to a negatively charged activating surface.**
- **Factor XII is autoactivated into XIIa, which has several substrates:**
  1. **factor XI, which activates factor IX.**
  2. **Kallikrein from prekallikrein (note the positive feedback activation loop).**
  3. **HMW kininogen releasing bradykinin (a peptide with potent vasodilator action).**
     - **Bradykinin is also generated by kallikrein.**
  4. **Other substrates: plasminogen (fibrinolysis) and complement system proteins.**

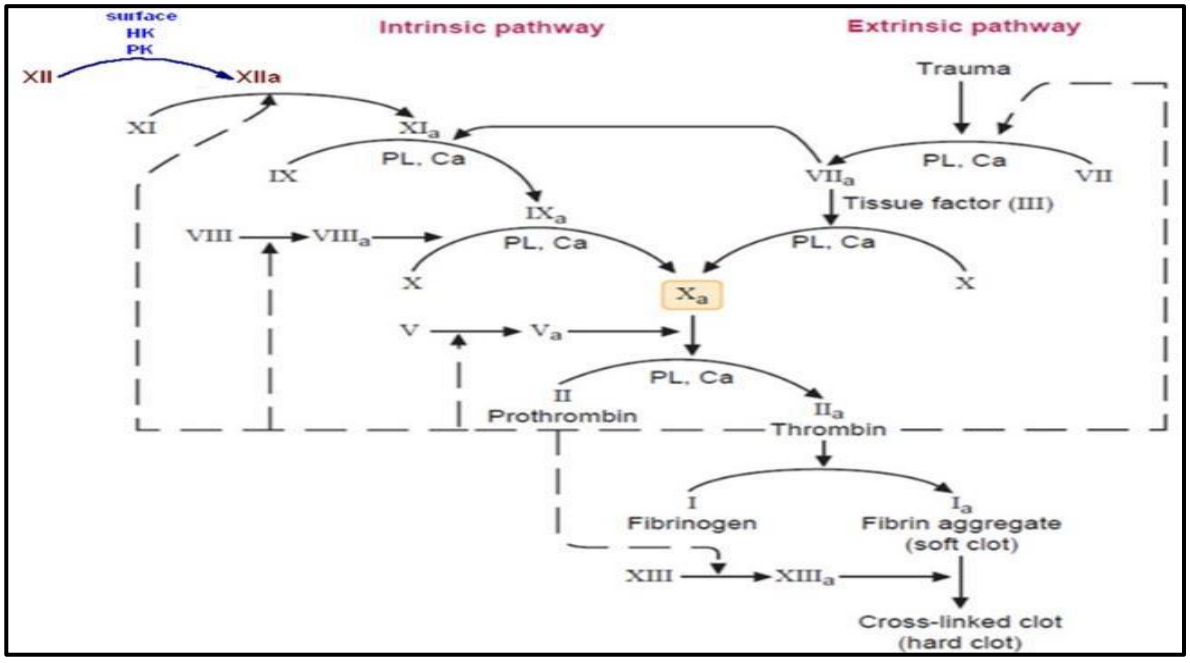
This picture explains what's written above:



HK, intact high-molecular-weight kininogen; HKc, cleaved high-molecular-weight kininogen; PK, prekallikrein; PKa, plasma kallikrein; polyP, polyphosphate

❖ Notes on the map below:

- **We said that TF binds to VII on platelets surface which activates factor X. Moreover, TF-VII complex activates factor IX (intrinsic pathway), which is already being activated by factor XI which was activated by factor XII.**
- **Factor XII is activated by prekallikrein on the surface of platelets.**
- **In extrinsic pathway: factor X is activated by TF-VII complex.**
- **In intrinsic pathway: factor X is activated by complex IXa.**



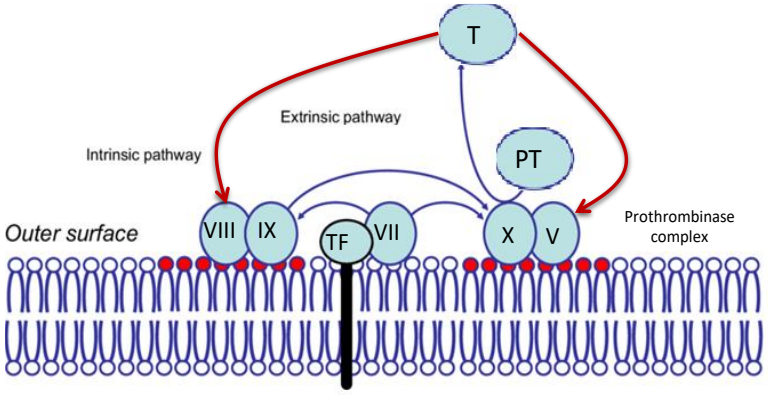
➢ THE TENASE COMPLEX

For factor X activation, it should be part of two complexes called the tenase complexes.

"Tenase: ten (10) / ase (enzyme)"

- **The activating complexes of factor X are called the "tenase" complexes.**
  - **The extrinsic tenase complex is made up of tissue factor, factor VIIa, and Ca^{2+}.**
  - **The intrinsic tenase complex contains the active factor IX (IXa), its cofactor factor VIII (VIIIa), and Ca^{2+}.**
    - **Tissue factor and factor VIIa also activate factor IX in the intrinsic pathway.**
    - **Xa activates prothrombin transferring it to thrombin.**

- Va and VIIIa are cofactors that increase the proteolytic efficiency of Xa and IXa, respectively.
  - Both factors V and VIII are activated by thrombin via a feedback mechanism.



➢ Von WILLBRAND FACTOR DEFICINECY

When von Willbrand factor is released from endothelial cells and platelets it binds with factor VIII on cell surface, as result it increases VIII half-life.

When von Willbrand factor is not being released (deficiency) , VIII half-life will be decreased.

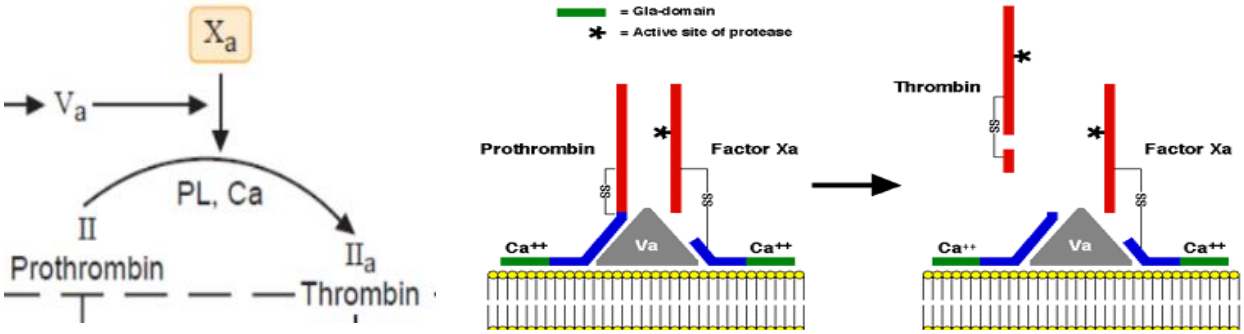
- **Factor VIII circulates in plasma bound to von Willebrand factor, which increases VIII half-life, and, when released, it gets activated.**
  - **von Willebrand factor deficiency is associated with decrease in the plasma concentration of factor VIII.**

➢ PROTHROMBIN ACTIVATOR

Factor X needs factor V to activate prothrombin.

If you remember from physio lectures, prothrombin is an unstable protein that can split easily into smaller compounds, one of which is thrombin. Factor V is important for factor X proteolytic activity.

- The complex of factor Xa/Va/Ca^{2+}/phospholipids, is the "prothrombinase complex".
- Factor Xa converts prothrombin to thrombin, which is accelerated by Va, platelets (or phospholipids), and calcium ions.
- Binding of calcium alters the conformation the Gla domains of these factors, enabling them to interact with a membrane surface of platelets.
- Aggregated platelets provide the surface upon which prothrombin activation occurs.



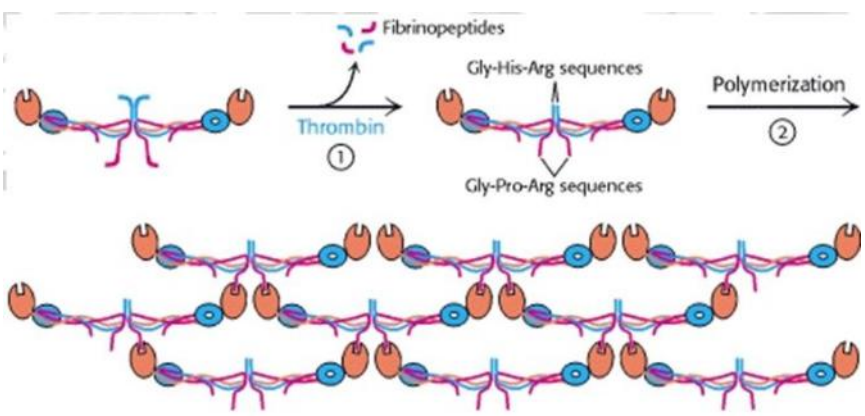
Thrombin is a protease, targets fibrinogen.

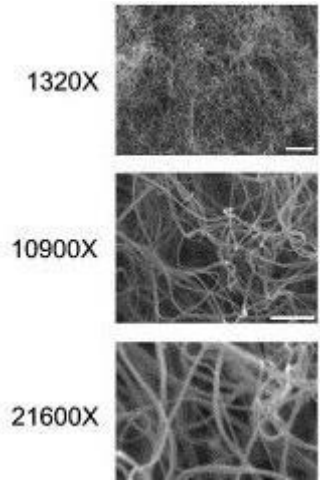
➢ Formation of a *soft* fibrin clot

- Thrombin cleaves fibrinogen releasing fibrinopeptides.
  - Fibrinogen is a two triple-stranded helical protein held together by disulfide bonds.

Fibrinogen is composed of 3 strands; those strands are separated molecules (the do not have interactions between each other) because of fibrinopeptides. What thrombin does is removing these peptides converting fibrinogen to fibrin.

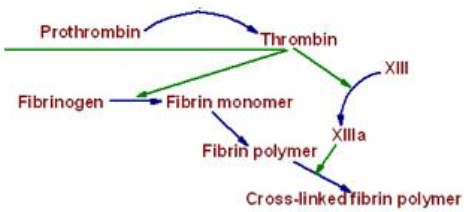
- **Fibrin molecules create electrostatic attractions among each other facilitating the aggregation of the monomers into a gel consisting of long polymers (called soft clot).**
- **The clot resulting from aggregation of fibrin monomers is referred to as the "soft clot “.**

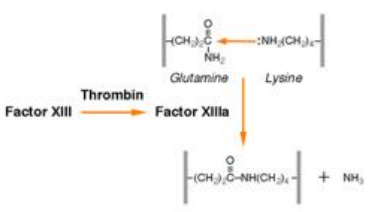


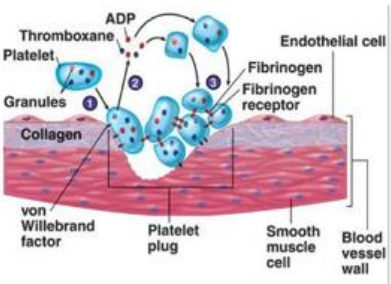


➢ THE FORMATION OF A HARD CLOT BY FACTOR XIII.

- **Factor XIII is a transglutaminase that is activated by thrombin.**
- **Factor XIIIa catalyzes a transglutamination reaction that causes a covalent cross-linking reaction between a glutamine of one fibrin monomer to a lysine of an adjacent fibrin monomer.**
    - **It also cross-links the fibrin clot to adhesive proteins on the endothelial tissue and to the platelet surfaces strengthening the platelet plug.**
    - **The cross-links strengthen the fibrin mass, forming the "hard clot “**



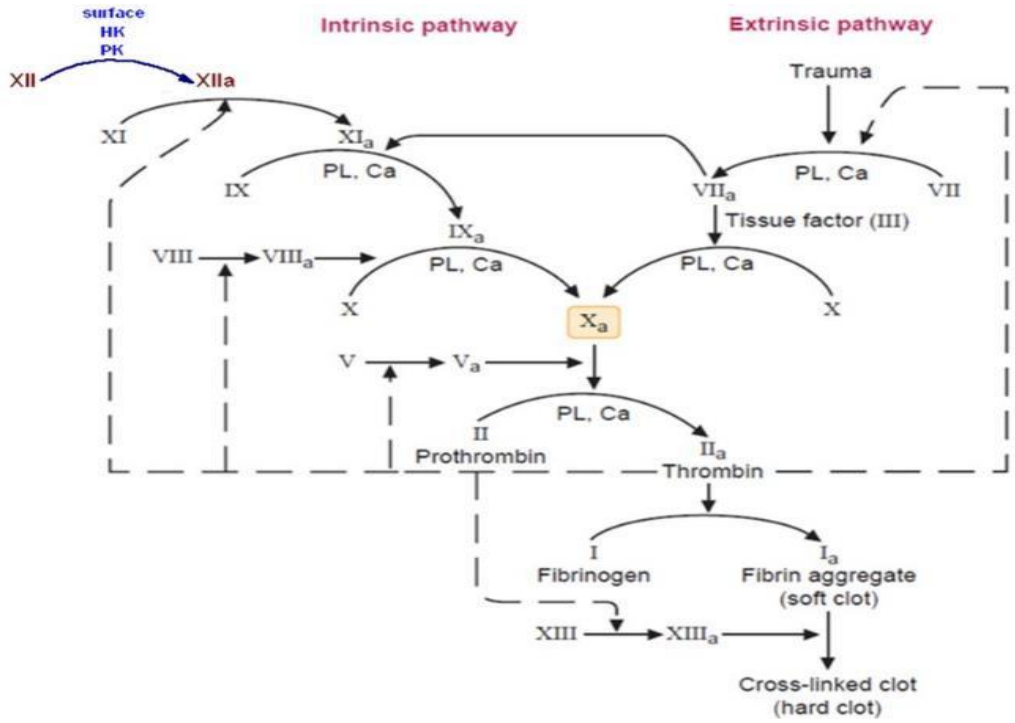




➢ AMPLIFICATION OF COAGULATION REACTIONS

This process is amplified through process steps & thrombin positive feedback activation.

- **The sequential enzymatic activation allows for amplification.**
- **Amplification also results from positive feedback reactions by thrombin.**
- **These include activation of V, VII, VIII, and XI by thrombin.**



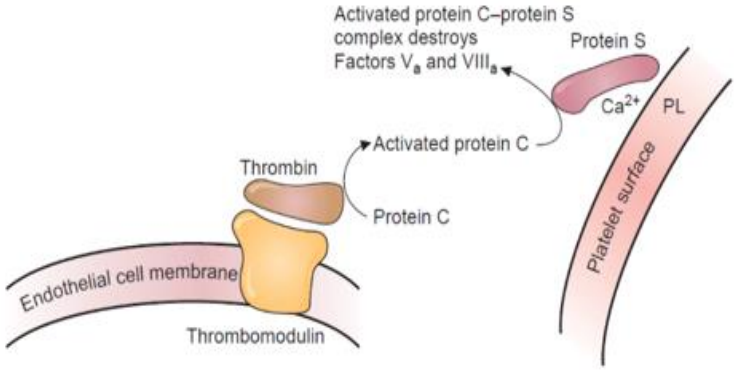
ANTI-CLOTTING FACTORS

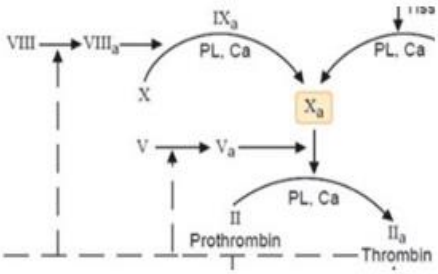
➢ PROTEIN C & PROTEIN S

Thrombin binds to thrombomodulin which activates protein C. Activated protein C binds to protein S on cell surface. Both proteins are dependent on vitamin k.

This complex degrades factors V & VIII, remember that those factors activate clotting pathway, which results in reduced factor X and thrombin activation slowing down the clotting pathway.

- **Thrombin binds thrombomodulin on the surface of endothelial cells.**
- **Thrombin can then activate protein C, which forms a complex with protein S, <u>both of which are vitamin K-dependent cofactors</u>.**
- **The complex degrades factors V and VIII.**



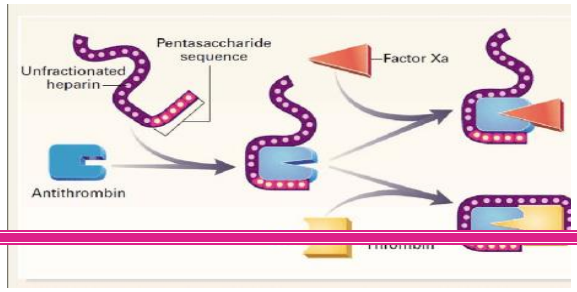


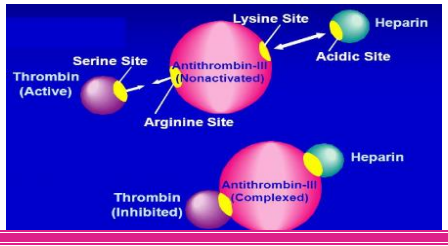
➢ ANTITHROMBIN III

Inhibitor of multiple factors and it's activated when these factors are complexed with tissue factor.

Antithrombin III needs heparin sulfate for activation.

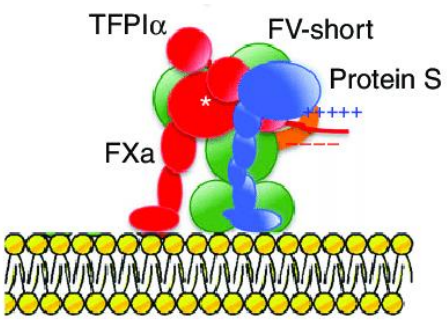
- **Antithrombin III is a protease inhibitor of thrombin as well as an inhibitor of IXa, Xa, XIa, XIIa, and VIIa when complexed with TF.**
- **Heparin sulfate, a polysaccharide synthesized by mast cells and present on the surface of endothelial cells, binds to antithrombin III, promoting binding to its substrates.**

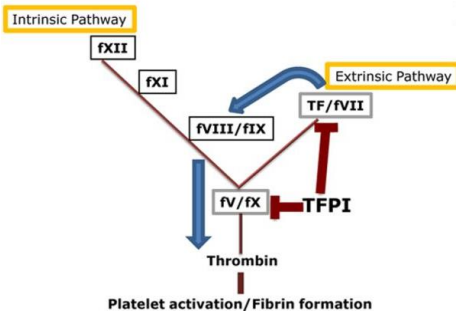




➢ TISSUE FACTOR PATHWAY INHIBITOR

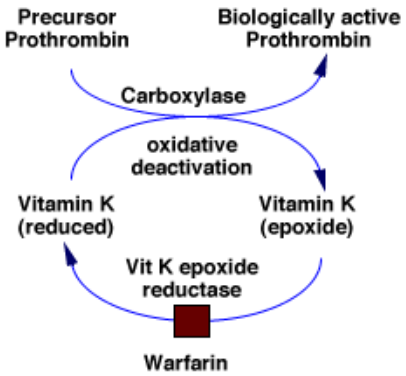
- **Tissue factor pathway inhibitor (TFPI) is a protein found in plasma lipoproteins and bound to the vascular endothelium.**
  - **It binds to and inhibits factor Xa.**
  - **The Xa-TFPI complex then interacts with the TF-VIIa complex and inhibits its activation of factors X and IX.**
  - **TFPI also inhibits Xa-activated Va resulting in inhibition of the pro-thrombinase complex.**
  - **Protein S binds to TFPI localizing it to membrane surfaces and enhancing the inhibition of Xa.**

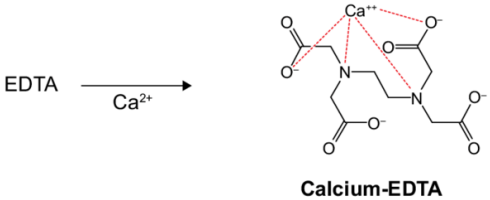




➢ Ca^{2+} CHELATORS AND VITAMIN K ANTAGONISTS

- **Non-enzymatic inhibitors of blood coagulation.**
- **Ca2+ chelators are chemicals called EDTA, found in tubes. They bind to ca2+ ions taking them from blood preventing coagulation.**
- **Warfarin inhibits reductase, as a result activated vitamin k cannot be regenerated, carboxylase enzyme doesn't function which inhibits coagulation (through inhibition of GLA carboxylation).**
  - **Blood clotting can be prevented by addition of Ca^{2+} chelators and vitamin K antagonists such as the drug warfarin, which inhibits the reduction of vitamin K and thereby prevents the synthesis of active prothrombin and factors VII, IX, and X.**





Calcium-EDTA

DEGRADATION OF FIBRIN CLOT

➢ CLOT DISSOLUTION

Clots must be dissolved (not only removed, since if they become free, they will clog another vessel).

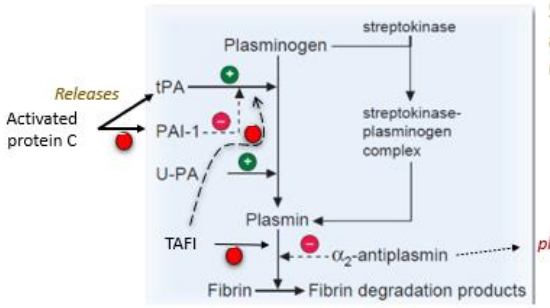
Dissolution happens through group of proteases.

- **It is important to prevent clot formation when not needed by anti-clotting factors and to dissolve a clot when formed.**
- **Clot dissolution starts concomitant with its formation.**

➢ THE FIBRINOLYTIC SYSTEM

- **Removal of fibrin clot is highly organized; the most important enzyme is plasmin which comes from plasminogen by proteolytic activation.**
- **Plasminogen is not activated unless it binds to fibrin clot.**
- **Plasminogen is activated by tissue plasminogen activator (tPA) which is activated by protein C.**
- **Plasminogen activation is controlled by an inhibitor (PAI-1).**
- **Activated protein C inhibits (PAI-1) to accelerate formation of plasmin.**
- **TAFI inhibits the process of activation tPA, which prevents fibrinolysis.**
- **When plasmin is released from clot, anti-plasmin is released inhibiting plasmin, preventing it from destructing another tissue.**

- **Plasmin is a protease formed from plasminogen and is responsible for fibrinolysis where it binds to fibrin and catalyzes its hydrolysis.**
    - **Plasminogen has a high affinity for fibrin clots.**
- **Thrombin activatable fibrinolysis inhibitor (TAFI) is a carboxypeptidase that removes the N-terminal lysine residues and prevents fibrinolysis.**



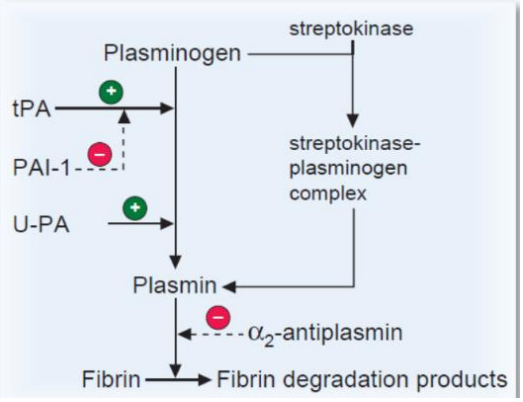
Streptokinase, a regulatory protein isolated from streptococci, allows autoactivation of plasminogen in blood, resulting in degradation of fibrinogen as well as fibrin.

but not when plasminogen/plasmin are clot-bound

➢ UROKINASE

Activates conversion of plasminogen to plasmin, so it's used to remove clots in certain patients.

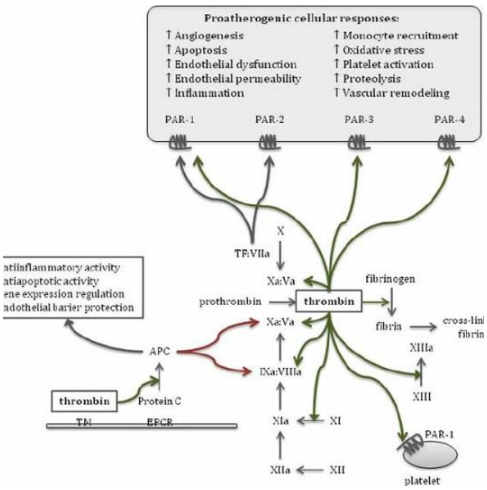
- **Urokinase (plasminogen activator) is a protease that is formed from the zymogen pro-urokinase.**
- **It is a potent plasminogen activator and is used clinically.**



➢ ROLES OF THROMBIN

- **Thrombin is multifunctional:**

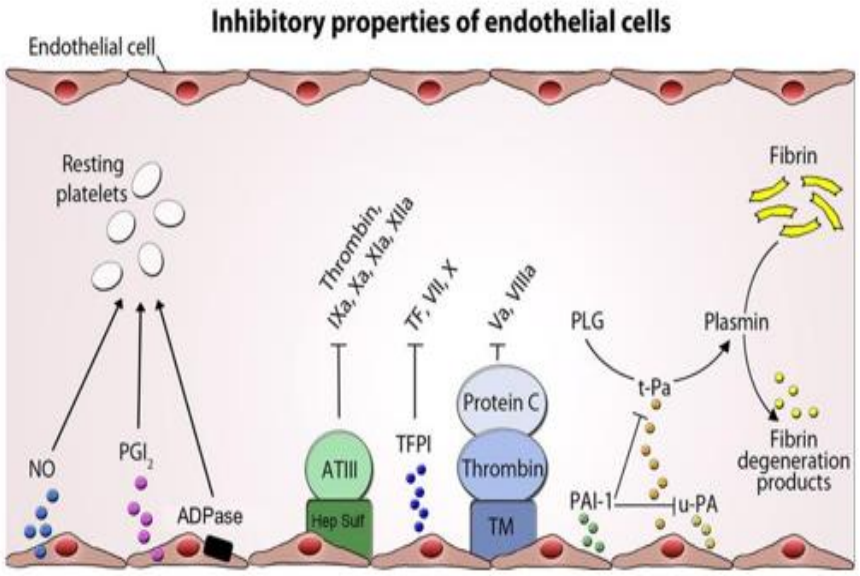
- **Platelet recruitment**
- **Amplification of the coagulation complex**
- **Formation of soft clot**
  - **Proteolytic cleavage of fibrinogen**
- **Formation of hard clot**
  - **Activation of factor XIII**
- **Attenuation of its own activity (slowing process of coagulation)**
  - **Activation of protein C**
- **Other actions**
  - **Binding to its receptor on the surface of platelets induces vascular remodeling (e.g. angiogenesis) and inflammation.**



➢ ROLE OF ENDOTHELIAL CELLS IN COAGULATION

- **Endothelial cells release NO & PGI2 (vasodilators), ADPase (which breaks down ADP and prevents platelets adhesion and aggregation.**

This picture and what's written in red are important.



- ECs release NO, prostacyclin (PGI2), and ADPase, which inhibit platelet adhesion and aggregation.
- Membrane-bound heparin sulfate binds to antithrombin III (ATIII) inactivating several coagulation factors.
- ECs express tissue factor pathway inhibitor (TFPI), which inhibits tissue factor (TF) and, consequently, factors VII, IX, and X.
- Thrombomodulin (TM) binds thrombin activating protein C, which degrades factors Va and VIIIa.
- ECs balance fibrin accumulation and lysis by releasing plasminogen activators, t-PA and u-PA, and their inhibitor (PAI).

Neubauer and Zieger. Endothelial cells and coagulation. Cell and Tissue Research (2021)

اللهم فرج على أهلنا في غزة، وامنحهم الصبر والقوة والعزيمة، اللهم اربط على قلوبهم، وداوي جرحاهم وتقبل شهداءهم واجعلهم في عليين.

لا تَنسوهم من الدعاء.