The Coagulation Cascade

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Introduction

- When there is an injury to the blood vessels, the body eventually will prevent the blood loss through a process known as the coagulation cascade.
- The coagulation cascade is a multistep process which goes from the formation of the clot after bleeding starts to the termination of the clot and ends with breakdown of the clot.
- The coagulation cascade also explains the site of action of various anticoagulants.
- Our presentation analyzes each step of this complex process.

Clot Formation

Steps of the Coagulation Cascade

PHASES OF THE HEMOSTATIC PROCESS

- Endothelial injury and formation of the platelet plug.
- Propagation of the clotting process by the coagulation cascade.
- Termination of clotting by antithrombotic control mechanisms.
- Removal of the clot by fibrinolysis.

FORMATION OF THE PLATELET PLUG

The functional response of activated platelets involves four different processes:

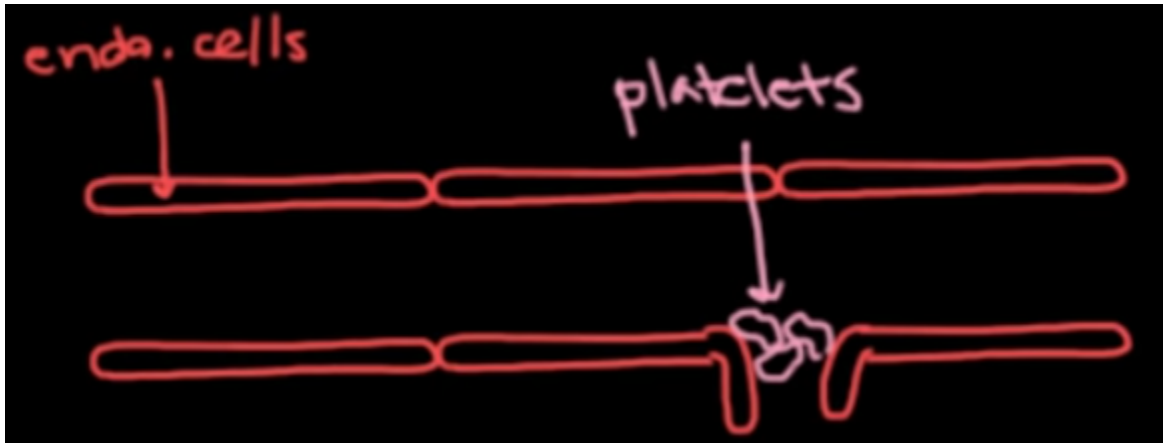
- Adhesion – The deposition of platelets on the subendothelial matrix
- Aggregation – Platelet-platelet cohesion
- Secretion – The release of platelet granule proteins
- Procoagulant activity – The enhancement of thrombin generation

Step 1 – Endothelial Injury

1. The endothelial cell wall lining blood vessel breaks open. The body starts the process of the coagulation cascade and the next step begins.

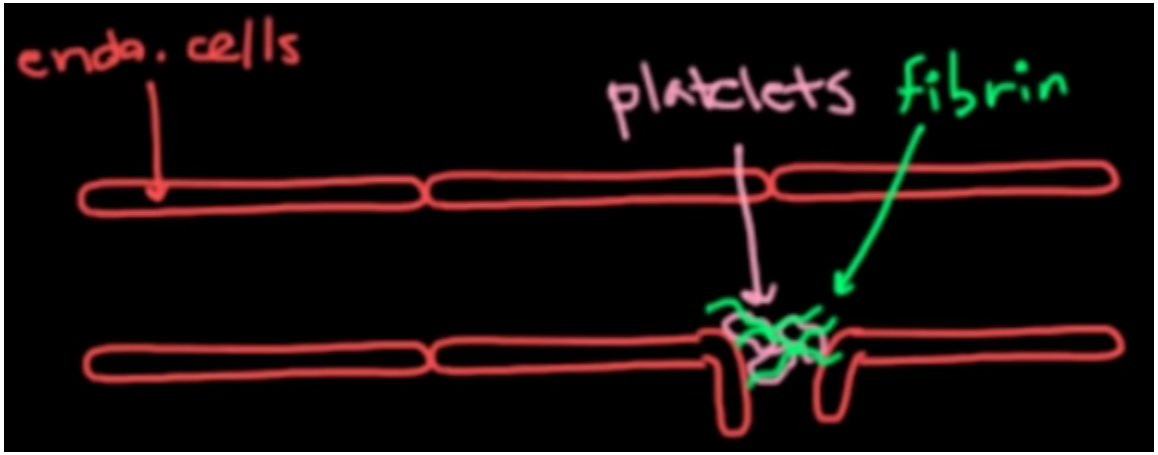
Step 2 – Formation of the Platelet Plug

2. Tiny platelets circulating body deposit in opening and form an initial plug.



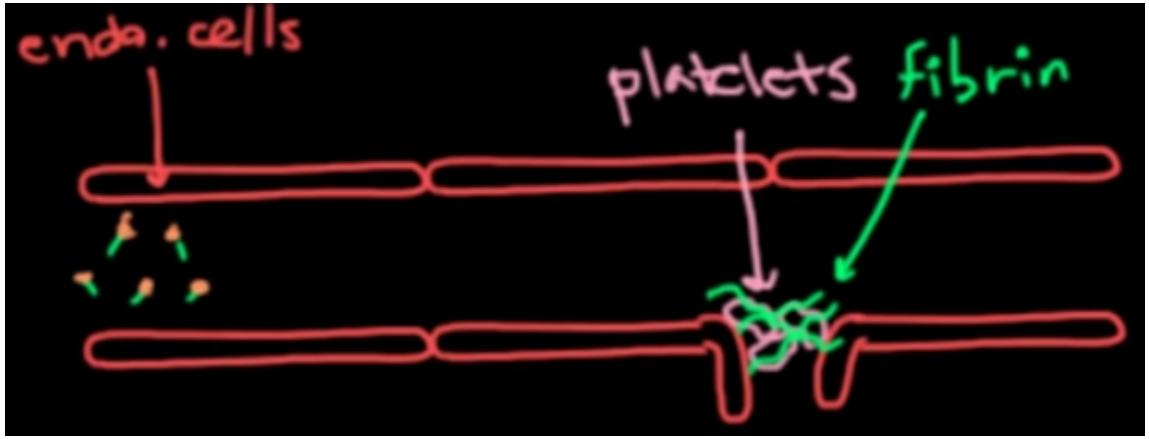
Step 3 - Propagation

3. Polymer fibrin strands act as a mesh over platelets to reinforce the wall.



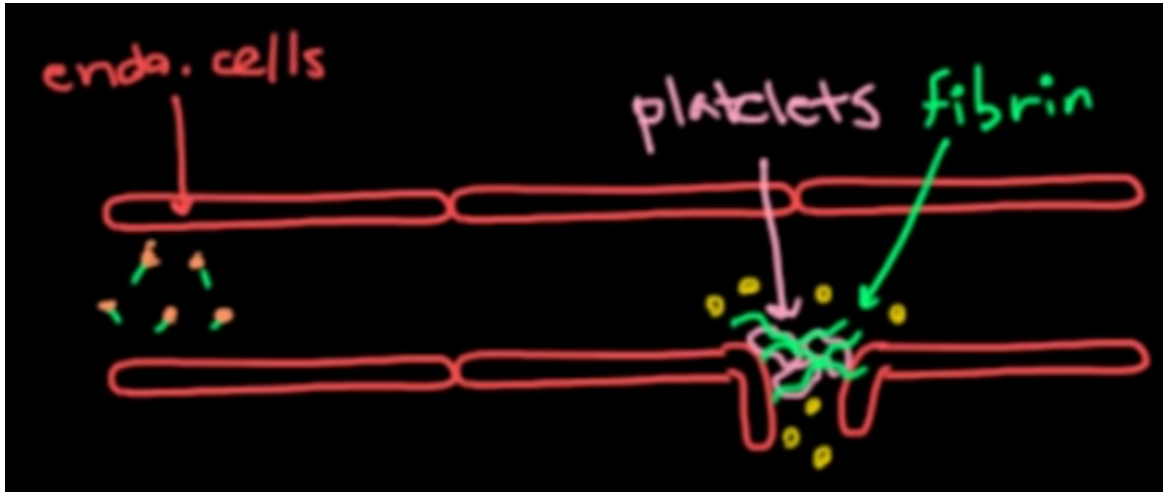
How Step 3 Happens

3A. Fibrinogen in the bloodstream doesn't react or interact with each other.



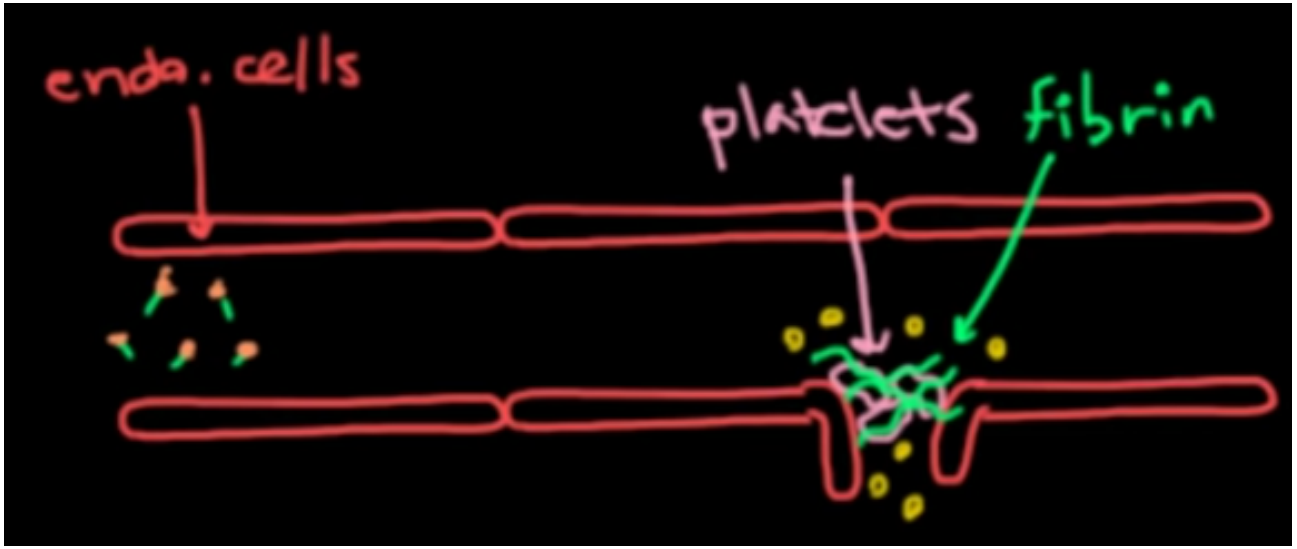
How Step 3 Happens

3B. Endothelial cells release proteins at the site of injury and blood exposes new proteins to fibrinogen.



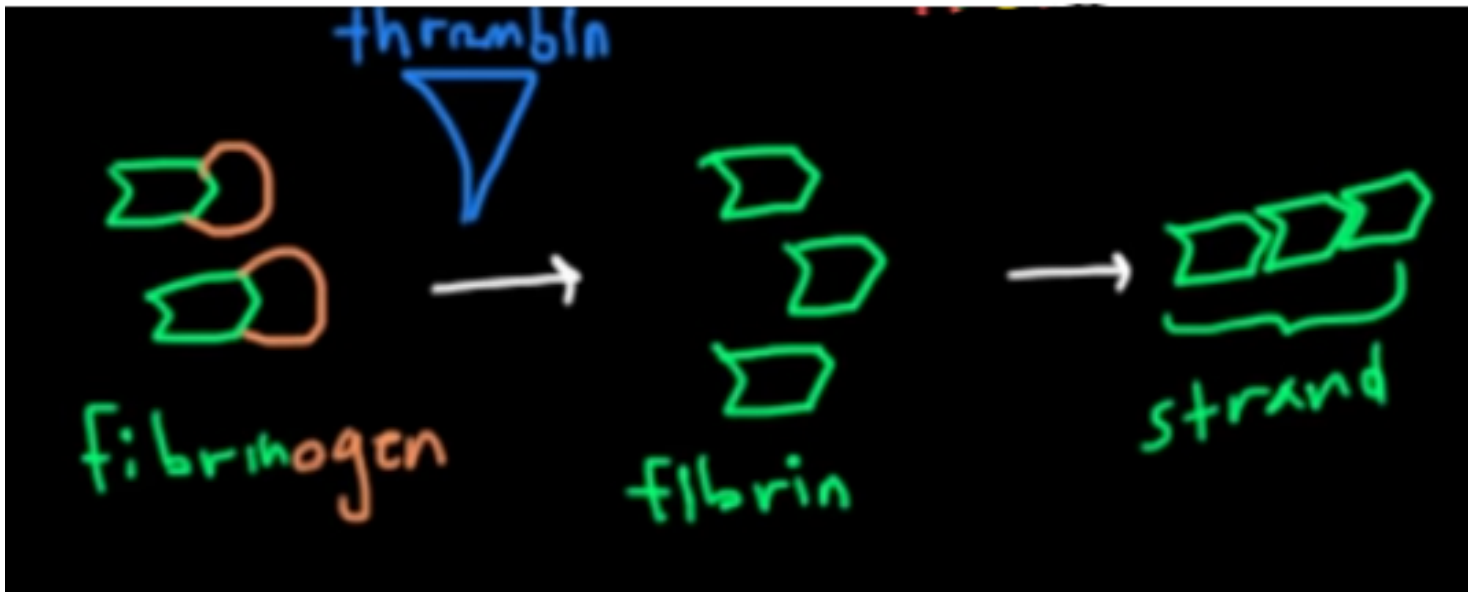
How Step 3 Happens

3C. New proteins eventually convert fibrinogen to fibrin, which in turn becomes fibrin strands.

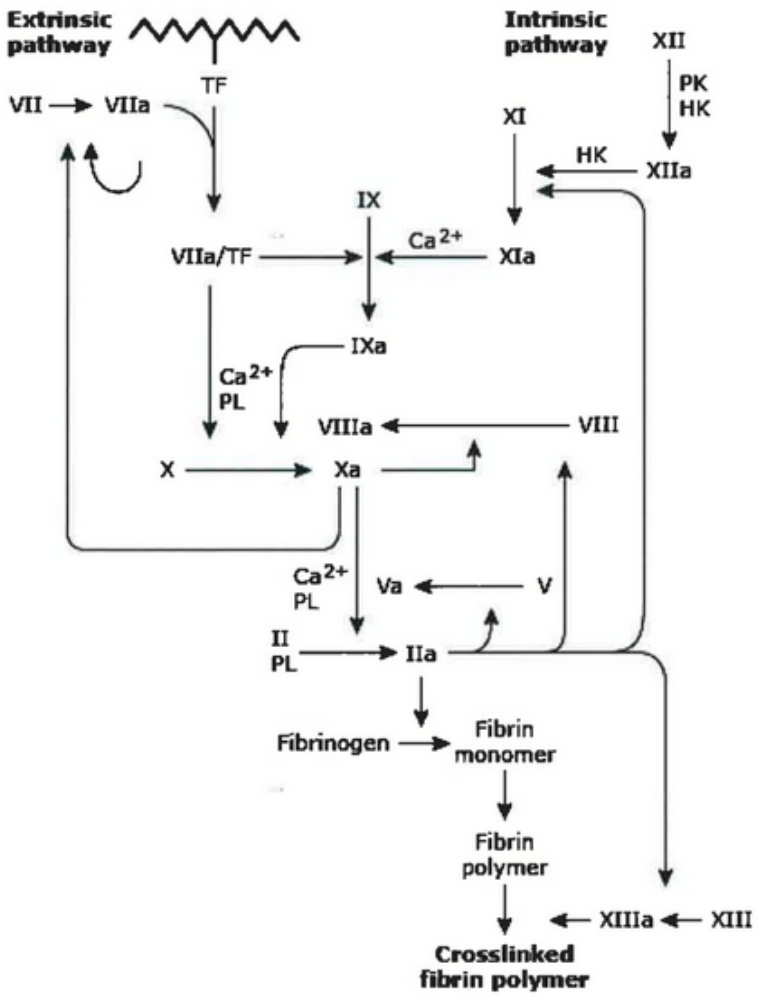


How Step 3 Happens

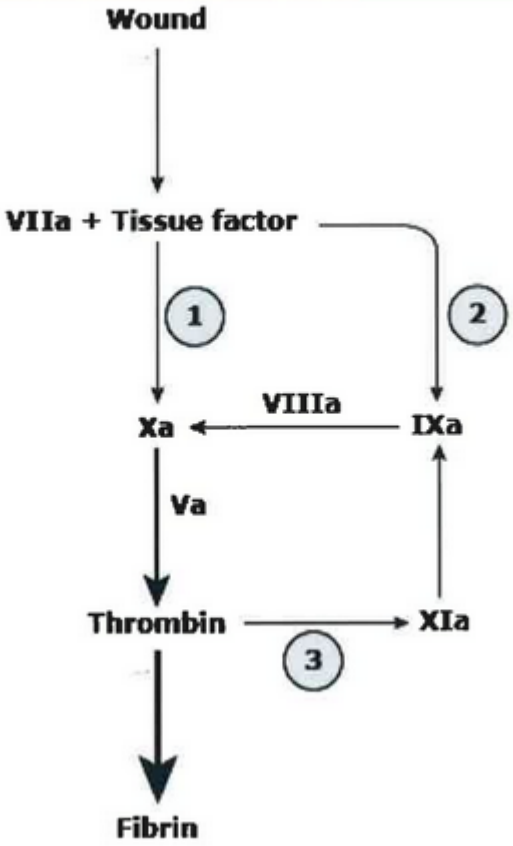
3D. These proteins call prothrombin.



Coagulation cascade detailed/traditional view



Coagulation cascade overview

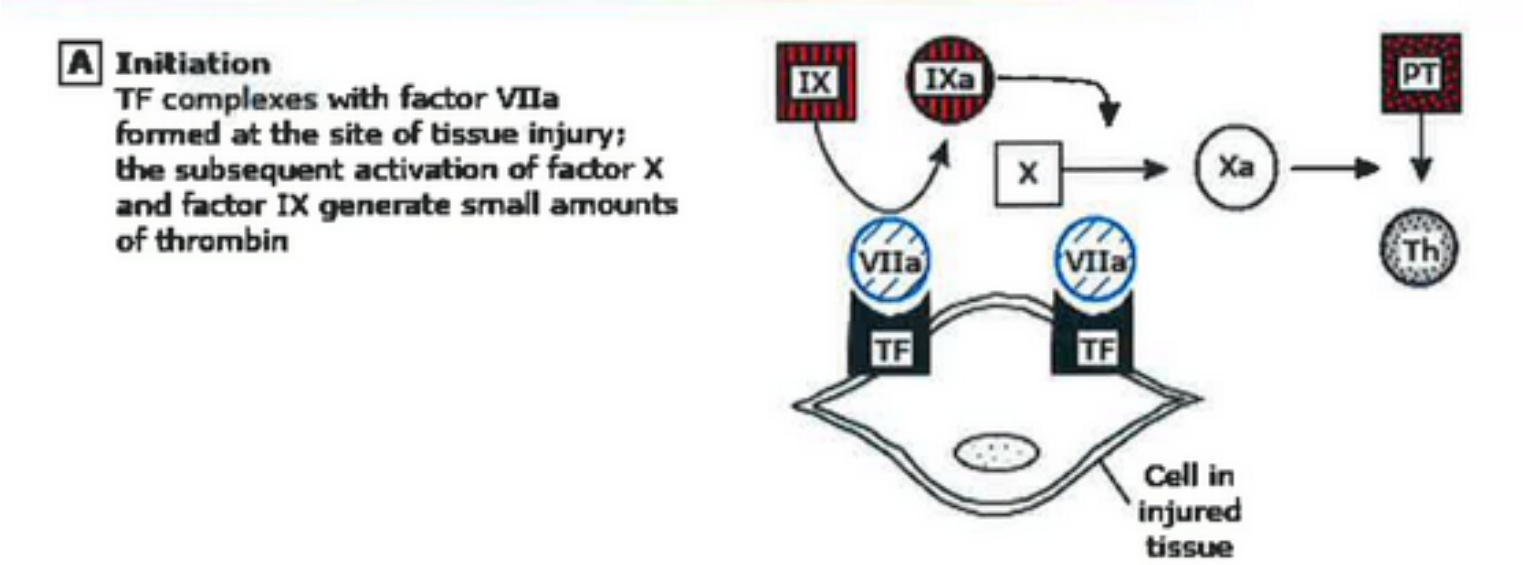


The Cascade

Extrinsic pathway (workhorse, gets most of the coagulation process done) is the “spark” to cascade.

It activates:

1. Tissue factor (Factor III, protein), which activates Factor VII.

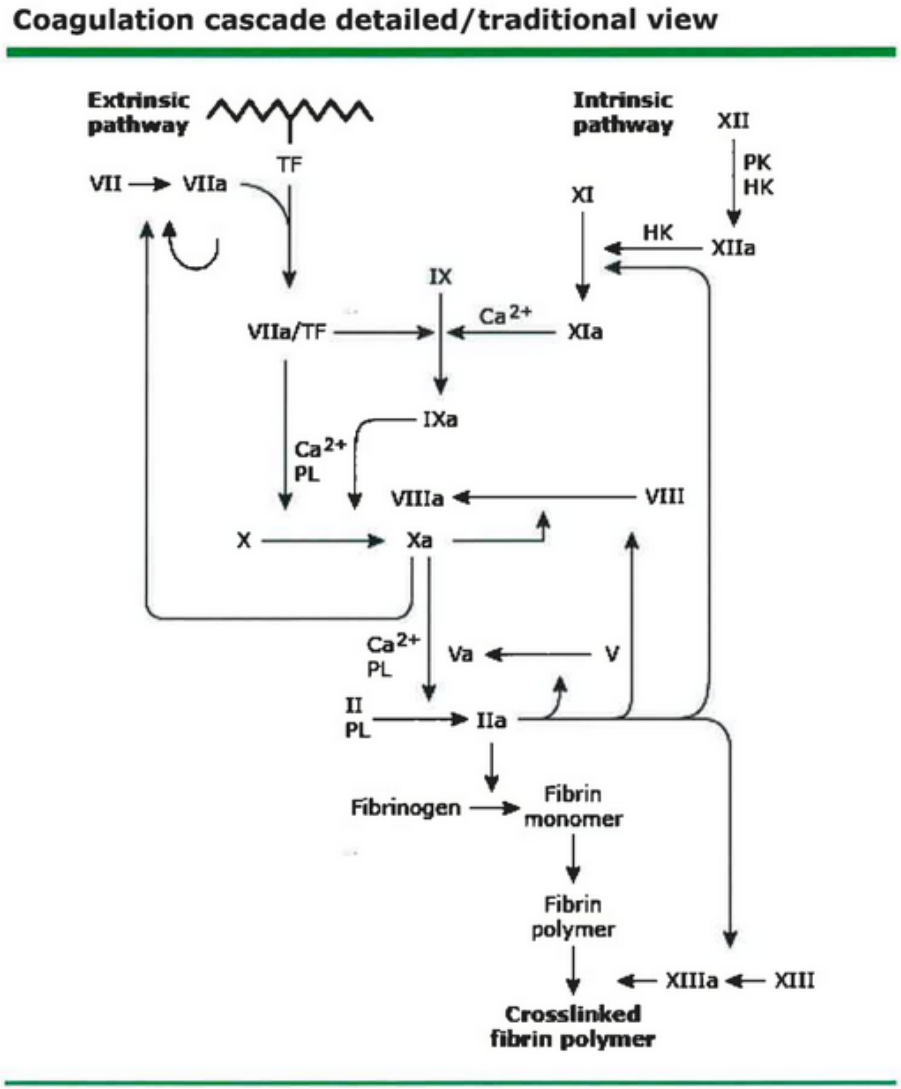


The Cascade (cont.)

2. Factor VII activates Factor X (which works with V), finally activating Factor II
3. Factor II, which is thrombin/prothrombin (which reactivates Factors V, VII, VIII, XI, and XIII) then activates
4. Factor I, fibrinogen/fibrin, which become fibrin strands. Fibrin strands get connected by
5. Factor XIII (which is activated by Factor II), which makes crosslinks between strands, creating a mesh, plugging the blood cells.

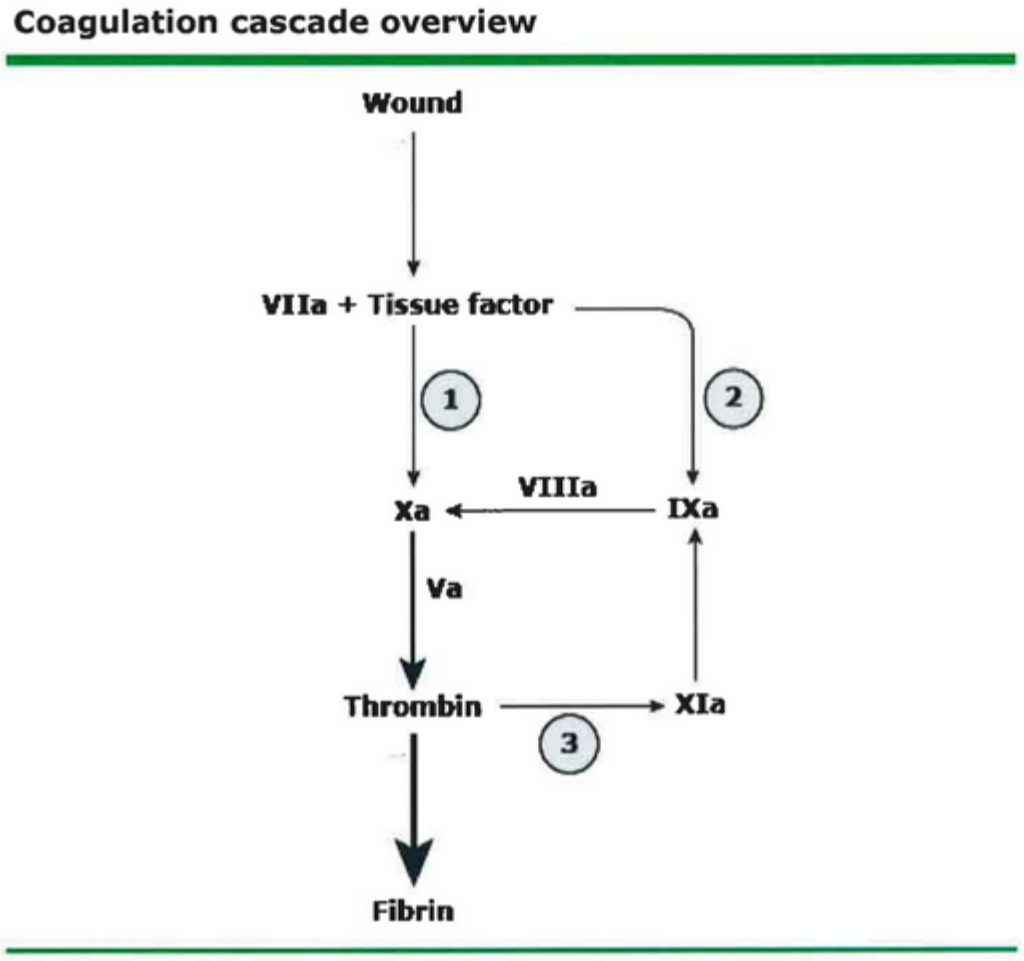
The Cascade (cont.)

1. In the intrinsic pathway, Factor XII activates Factor XI



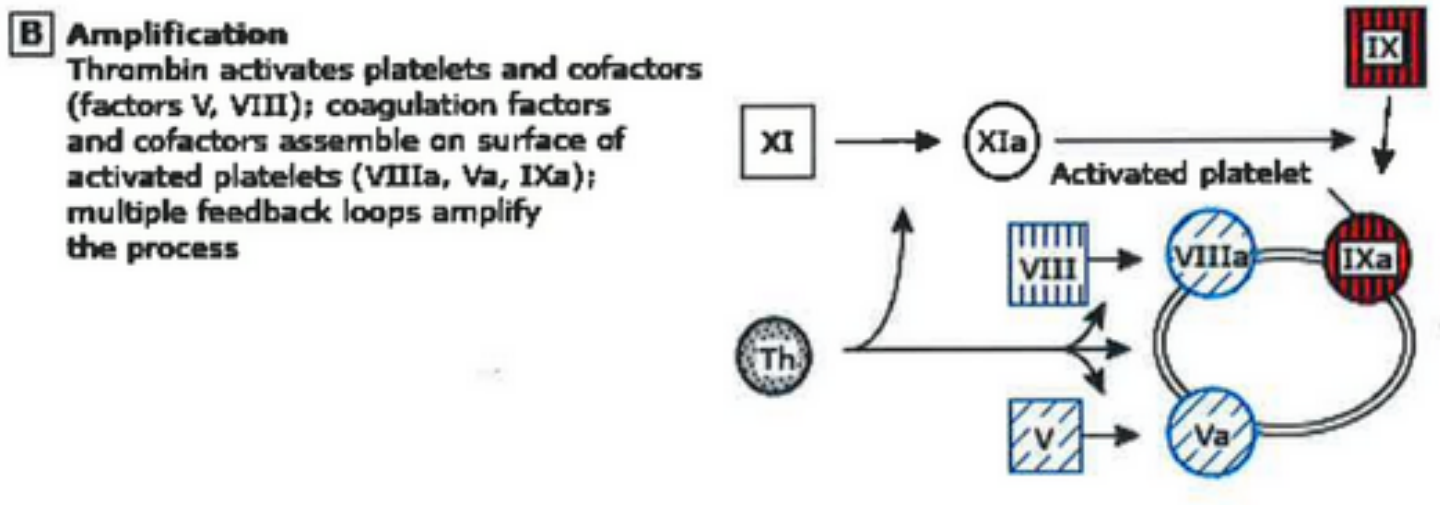
The Cascade (cont.)

2. Factor XI activates Factor IX (which works with Factor XIII), then activating
3. Factor X (which works with Factor II). The intrinsic pathway continues until it activates



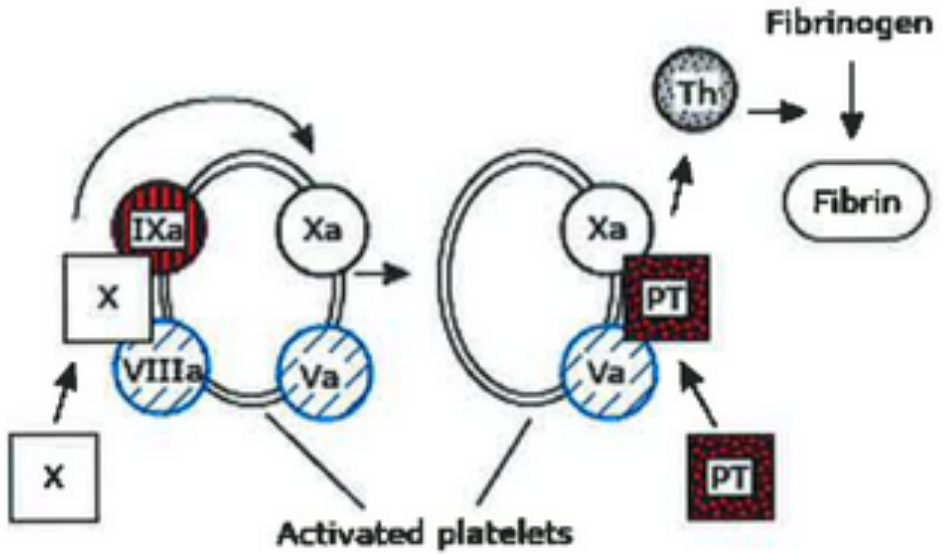
The Cascade (cont.)

4. Factor II, just like the extrinsic pathway, and Factor II does the rest. Additionally, Factor II starts up the intrinsic pathway by reactivating some factors, after it is activated by the extrinsic pathway.



The Cascade (cont.)

C **Propagation**
Assembled complexes continue cascade on surface of activated platelets; the prothrombinase complex converts prothrombin to thrombin which then converts fibrinogen to fibrin; this is followed by clot stabilization



The Termination of the Clot

Ending of the Cascade

There are some negative feedback loops to prevent your body from creating a bigger and bigger clot, due to how Factor II reactivates the cascade.

It's important for the cascade to terminate because if the clot continues to form, it could risk blocking the flow of blood in the body.

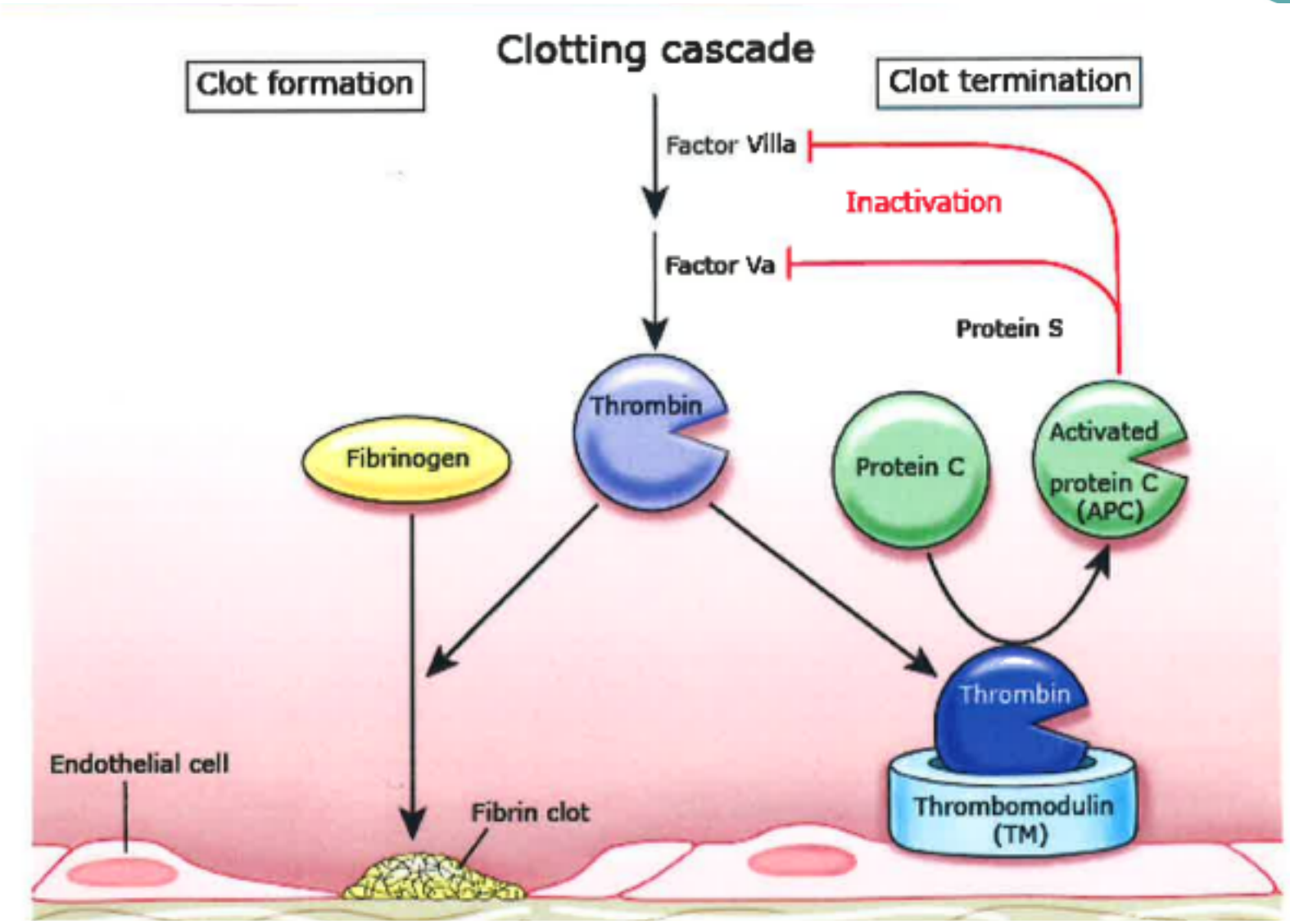
1. Arteries - conditions like strokes, heart attacks etc.
2. Veins - Deep vein thrombosis
3. Capillaries - e.g. conditions when people get chemotherapy

Termination of the Clot

Once a clot forms, the clotting process is terminated to prevent the clot from obstructing blood flow.

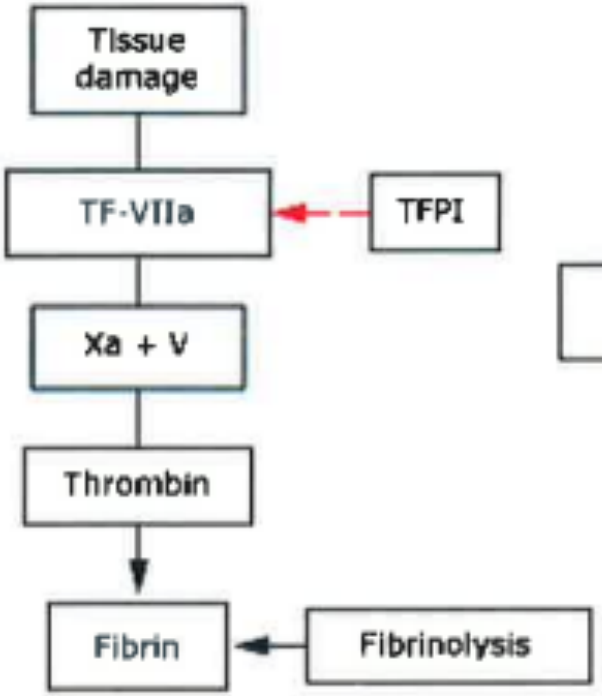
Natural anticoagulants are produced to stop the clotting process.

- Tissue Factor Pathway Inhibitors
- Protein C
- Protein S
- Antithrombin

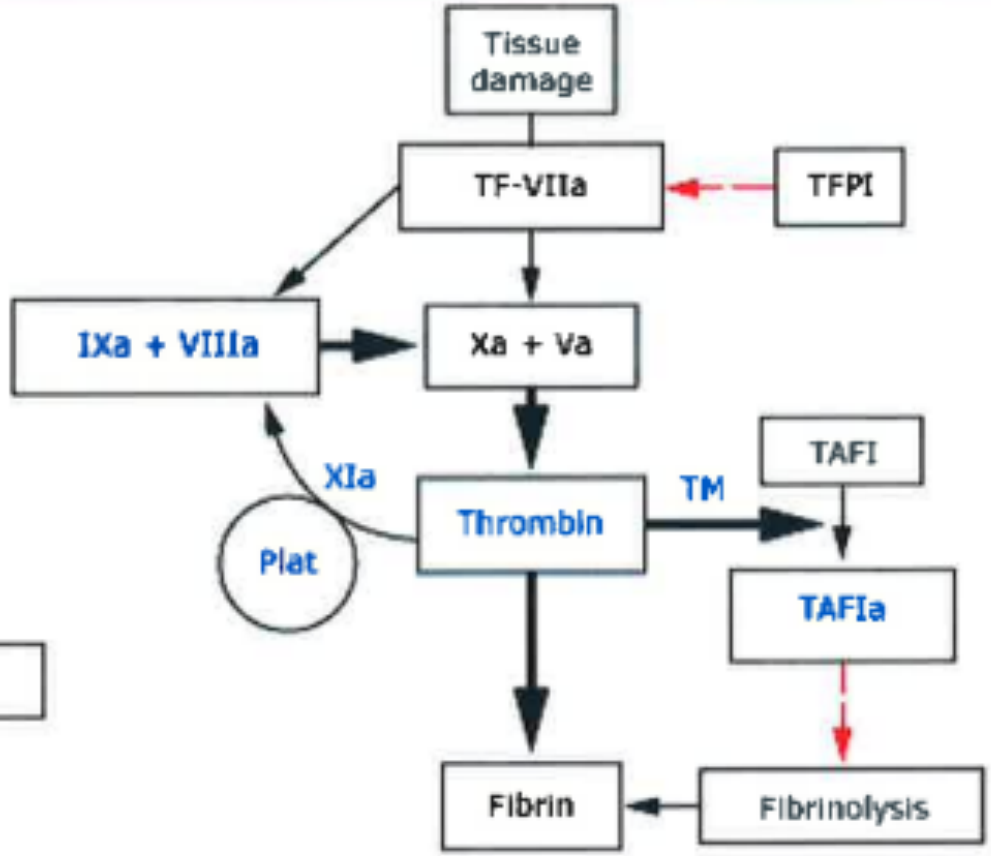

Clotting cascade
Clot formation
Clot termination
Factor VIIIa
Inactivation
Factor Va
Protein S
Thrombin
Fibrinogen
Protein C
Activated protein C (APC)
Thrombin
Thrombomodulin (TM)
Endothelial cell
Fibrin clot

Tissue Factor Pathway Inhibitor (TFPI)

- Natural Anticoagulant secreted by the endothelium
- Single chain polypeptide
- Inhibits Factor Xa, which is one of the most important factors in forming a clot



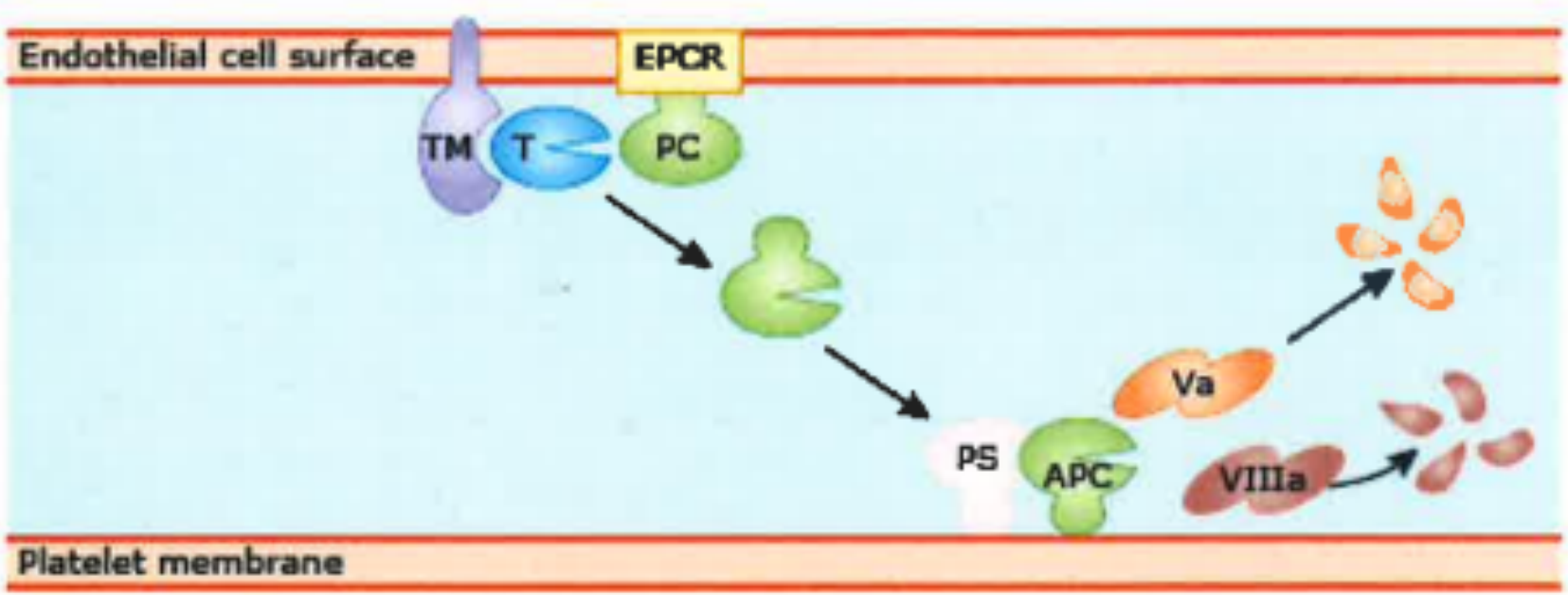
Initiation of Coagulation



Maintenance of Coagulation

Protein C and S

- Both are Vitamin K dependent glycoproteins
- Protein C activates Protein S



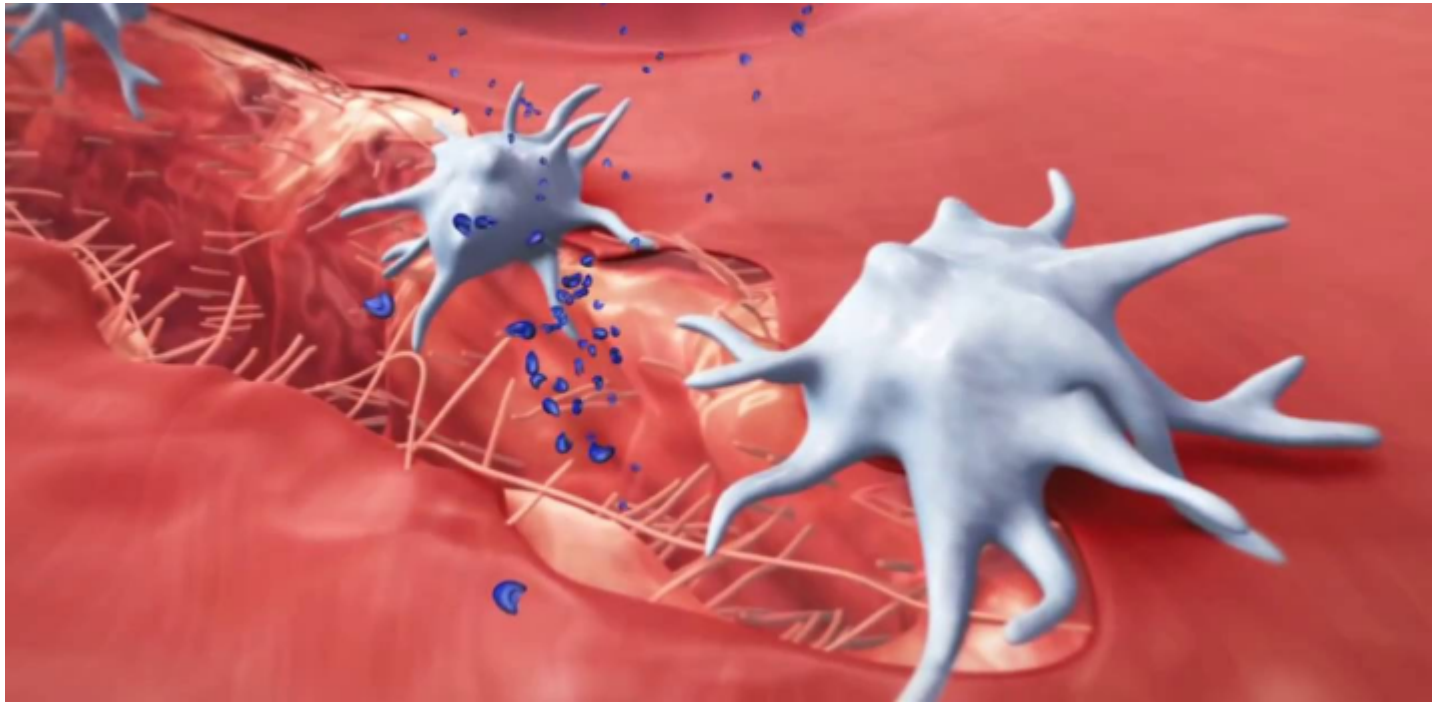
Antithrombin

- Natural anticoagulant
- Inhibits the activity of thrombin, which causes clotting
- Thrombin stimulates the production of antithrombin, which decreases the production of thrombin from prothrombin.
- Antithrombin also stops the activation of Factor X.

Removal of Clot by Fibrinolysis

What is Fibrinolysis?

Fibrinolysis remodels and degrades fibrin-rich thrombus with a tightly regulated process.



Purpose of Fibrinolysis

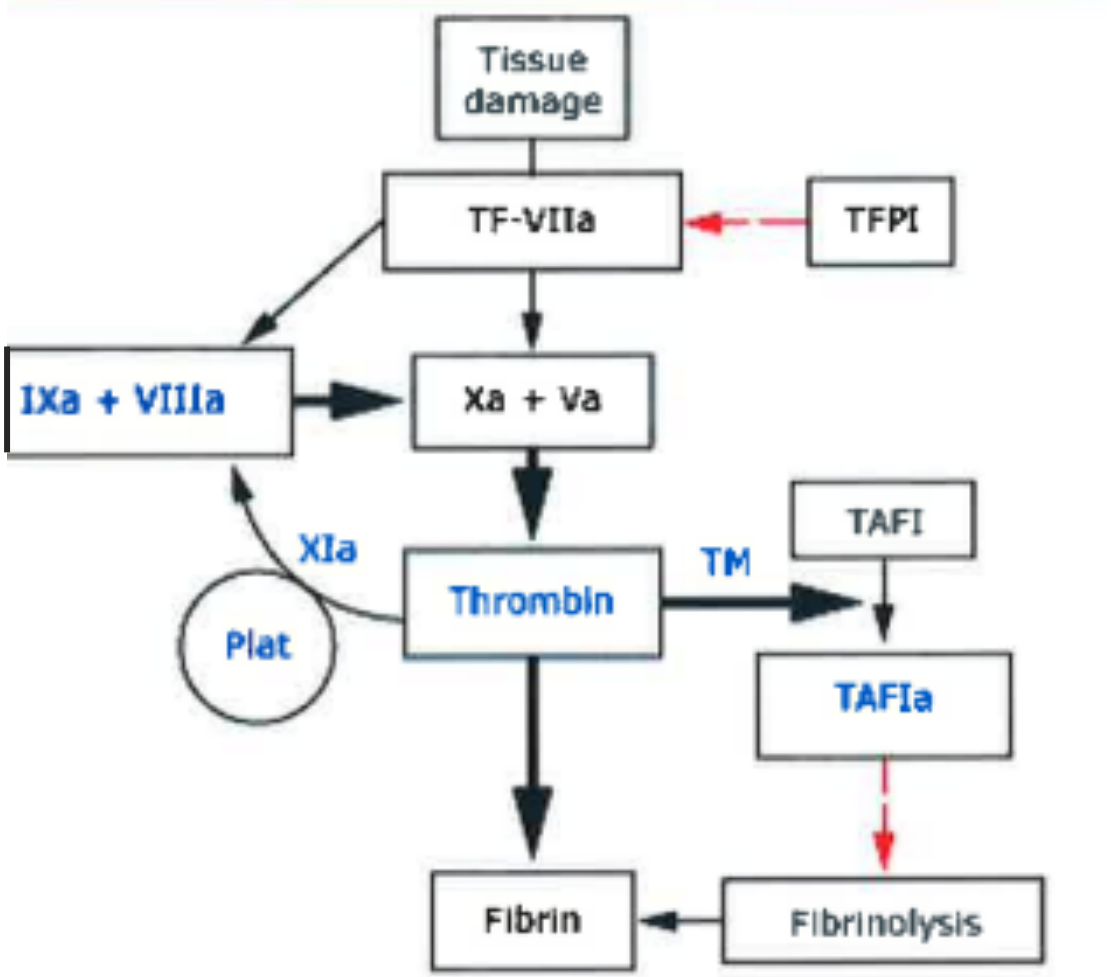
- Restores normal blood flow to the area of injury by dissolving a stable fibrin clot
- Converts plasminogen to plasmin
- Failure to complete fibrinolysis may contribute to development of a thrombus.

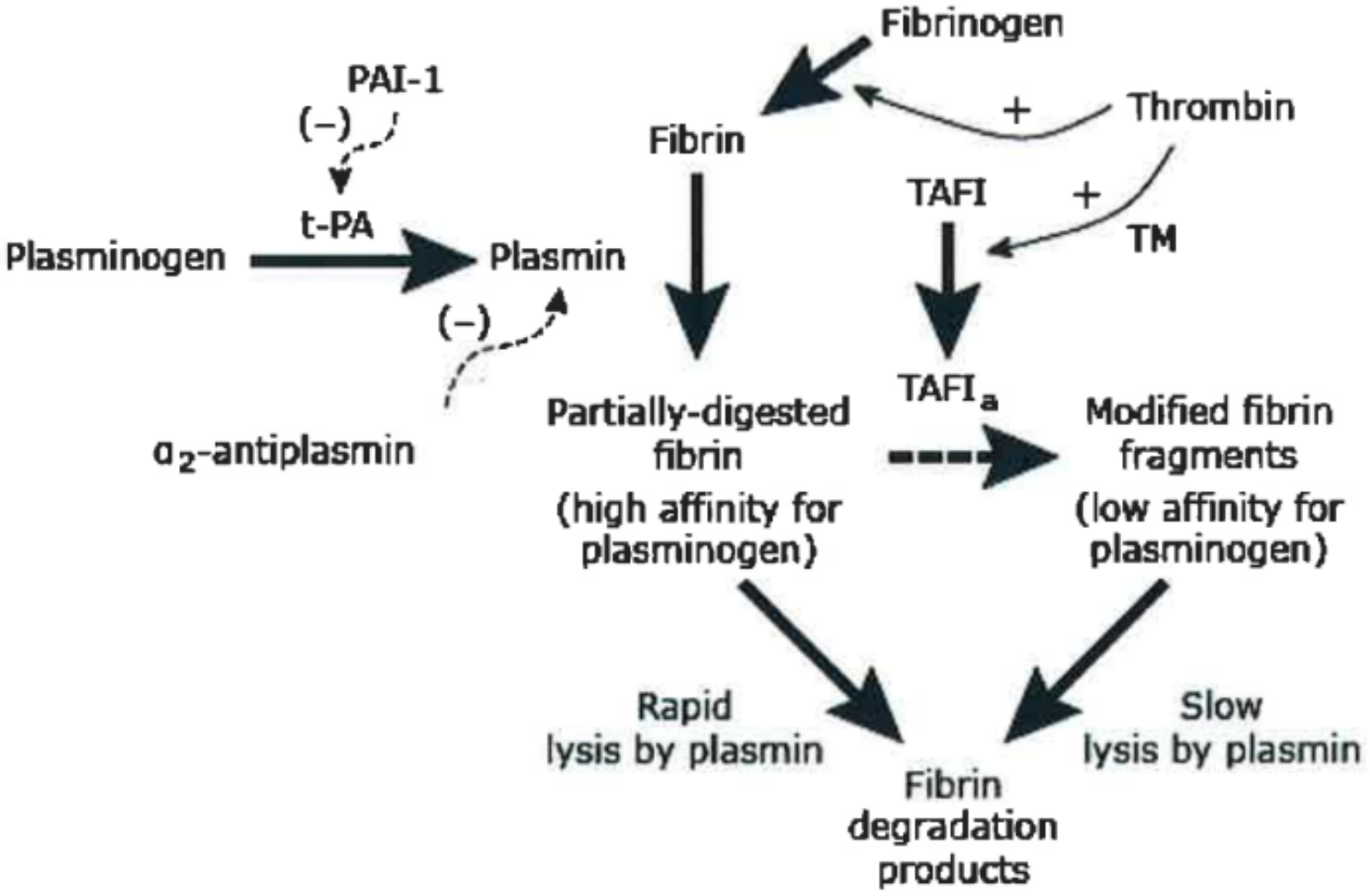
Steps of Fibrinolysis

- After the clot has been formed and the tissue repaired, fibrinolysis is activated through the attraction of plasminogen and tissue plasminogen activator (t-PA) to the lysine residues of fibrin.

Steps of Fibrinolysis (cont.)

- The t-PA catalyzes the conversion of plasminogen to plasmin.
- Plasmin digests the fibrin clot and yields fibrin degradation products.
- After the clot lysis is finished, the antiplasmin inactivates the plasmin once it enters the circulation.


Tissue damage
TF-VIIa
TFPI
IXa + VIIIa
Xa + Va
XIa
Plat
Thrombin
TM
TAFI
TAFIa
Fibrin
Fibrinolysis


Fibrinogen
PAI-1
(–)
+
Thrombin
Fibrin
t-PA
TAFI
+
Plasminogen
Plasmin
TM
(–)
TAFIa
Partially-digested fibrin
(high affinity for plasminogen)
Modified fibrin fragments
(low affinity for plasminogen)
α2-antiplasmin
Rapid lysis by plasmin
Slow lysis by plasmin
Fibrin degradation products

Reactions that Counteract Fibrinolysis

All of these reactions promote fibrin stability:

1. Factor XIIIa → cross-links fibrin
2. Thrombin-activatable fibrinolysis inhibitor → removes lysine residues from fibrin
3. Plasminogen activator inhibitor type 1 (PAI-1) → inactivates t-PA
4. A2-antiplasmin → inactivates plasmin

Primary Fibrinolysis

Primary Fibrinolysis

- Rapid clot breakdown because of excess t-PA
- Objective is to treat excessive plasmin activity
  - Antifibrinolytic agent is a common course of treatment

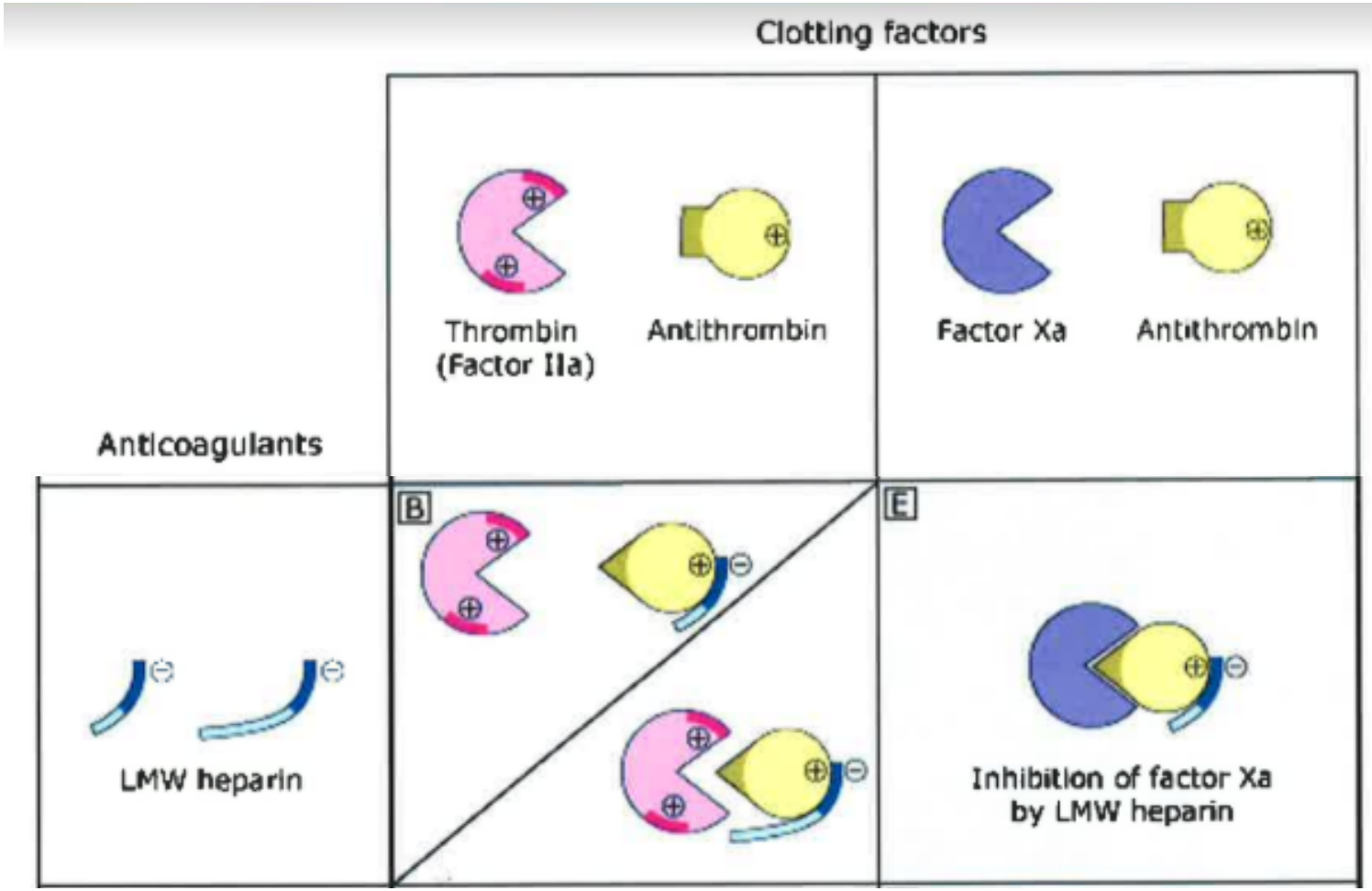
Secondary Fibrinolysis

Secondary Fibrinolysis:

- Result of hypercoagulability
  - increased breakdown of clots due to larger number of clots being formed
  - Reasons:
    A) Acquired
    B) Genetic
- Treatment = anticoagulant therapy

Application of Secondary Fibrinolysis

- Stroke is a very common and a very dangerous situation.
- It can happen due to many reasons but a blood clot is one of the most common causes.
- These changes happen suddenly without a warning and can cause long term disability or even death.
- Breaking the clot down in 6 hours or less is critical to save a patient's life, permanent damage and long term disability.
- t-PA is used on an emergency basis in every ER to save a stroke.


Clotting factors
Thrombin
(Factor IIa)
Antithrombin
Factor Xa
Antithrombin
Anticoagulants
B
E
LMW heparin
Inhibition of factor Xa
by LMW heparin

Summary and Conclusions

- The coagulation cascade is a crucial process because it prevents excess blood loss by making a clot in the blood vessels and terminating it, finally removing it once the walls have healed.
- There are many dangerous implications if any step of the coagulation cascade if there is any interference that prevents a step from happening.
- Coagulation cascade also gives an idea of where the various anticoagulants act, which helps in the synthesis of newer anticoagulant agents and their antagonists.

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