

# Coagulation Mechanisms

**Dr. Nervana Bayoumy**

Associate Professor  
Department of Physiology

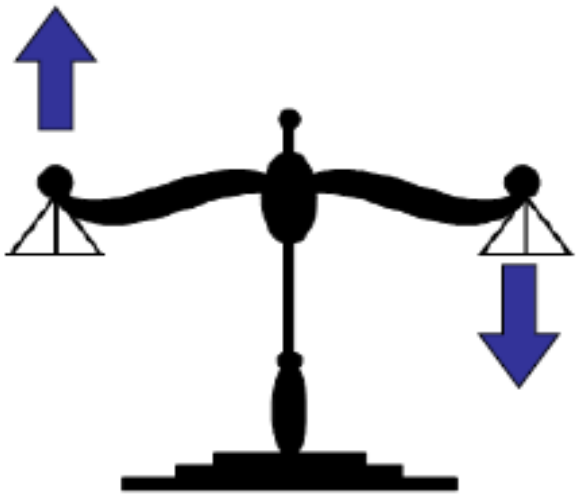
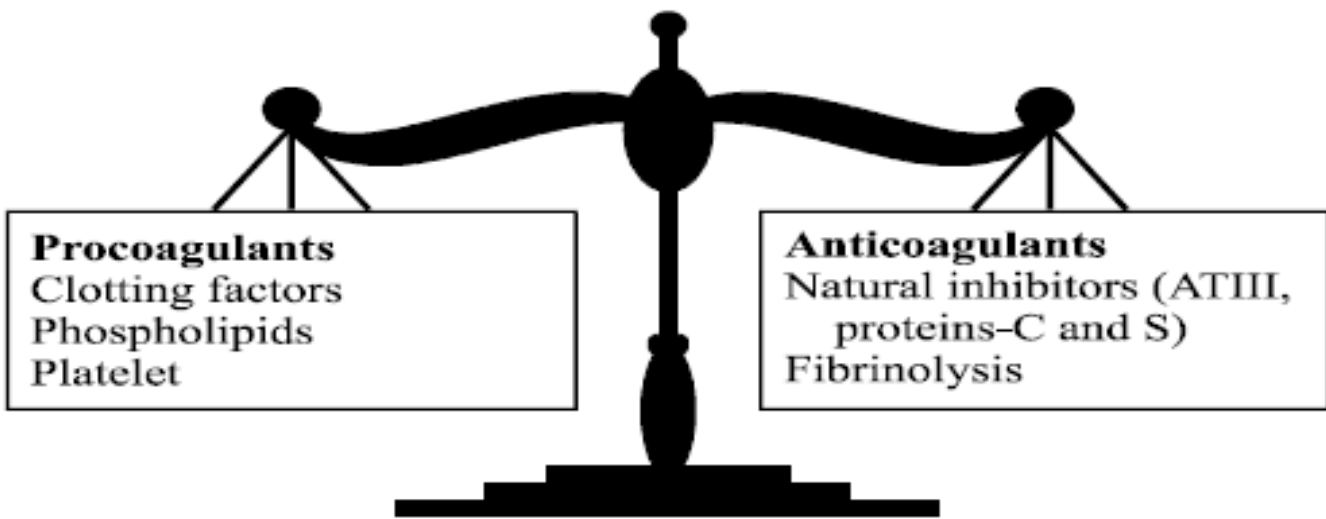
# Objectives

At the end of this lecture you should be able to:

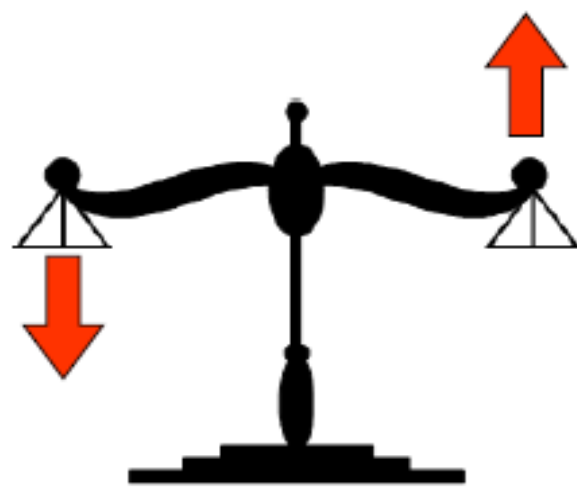
1. Recognize the different clotting factors
2. Understand the role of calcium ions during clotting cascades.
3. Describe the cascades of intrinsic and extrinsic pathways for clotting.
4. Recognize process of fibrinolysis and function of plasmin
5. Recognize some conditions causing excessive bleeding
6. Understand some important anticoagulants and their mechanism of action

# Mechanism of Blood Coagulation

- A crucial physiological *balance* exists between factors promoting coagulation (**procoagulants**) and factors inhibiting coagulation (**anticoagulants**).
- Coagulation of blood depends on the *balance* between these two factors.
- Disturbances in this *balance* could lead to **thrombosis** or **bleeding**



Thrombosis



Haemorrhage

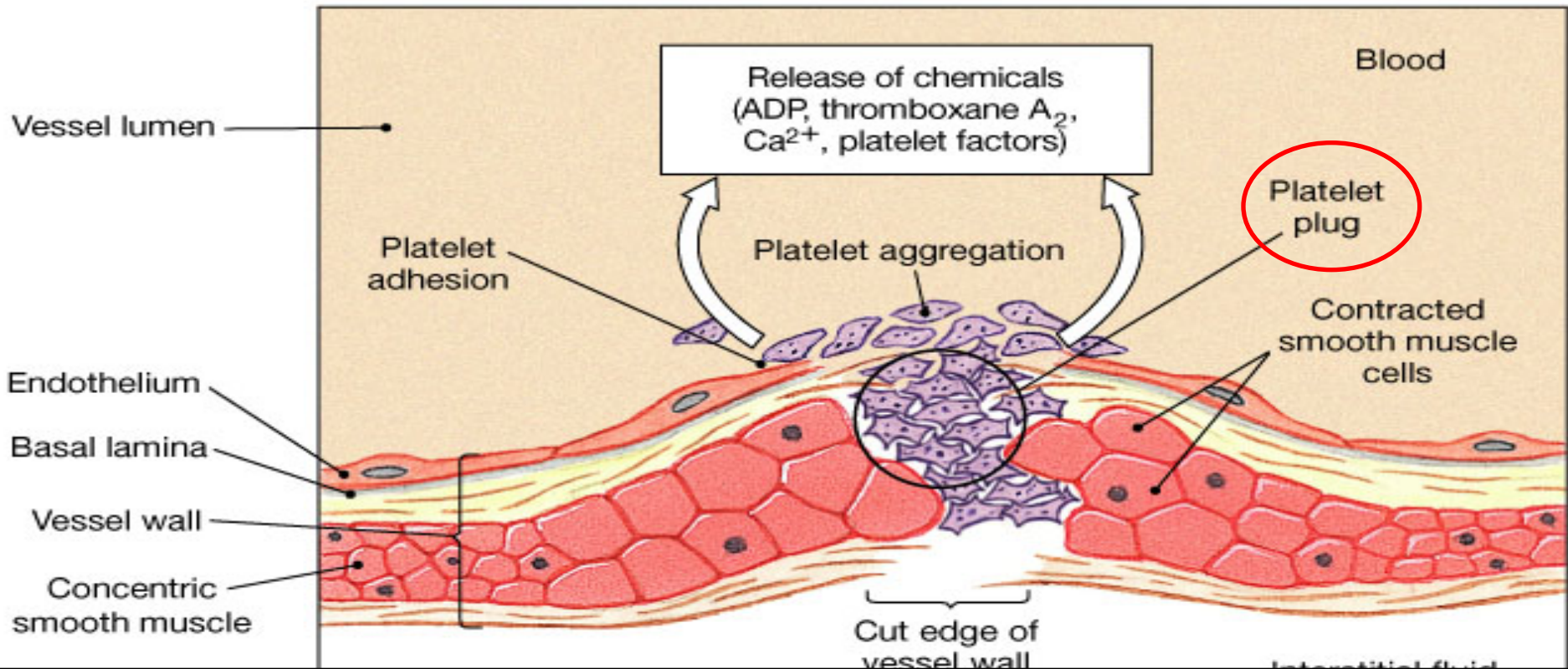
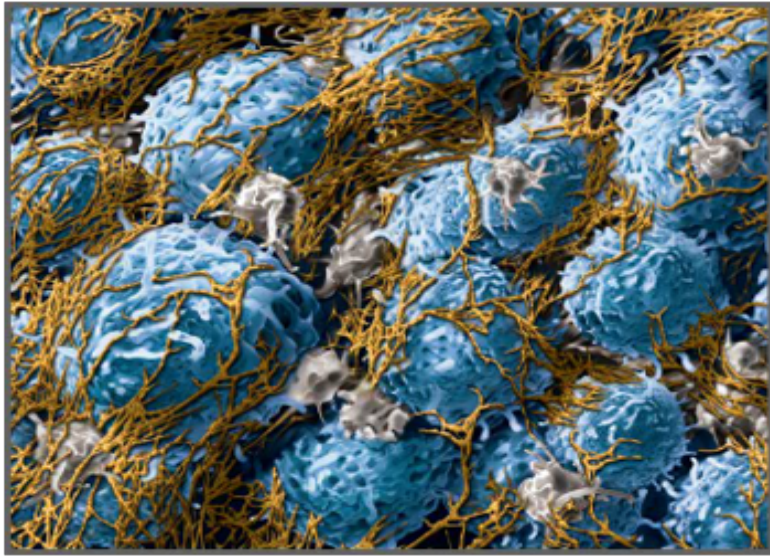
# Hemostasis:

prevention or stoppage of blood loss.

## Hemostatic Mechanisms:

1. **Vessel wall** (Vasoconstriction)
2. **Platelets** (Production and activation, Platelets Plug formation)
3. **Blood coagulation**  
Clot formation (intrinsic & extrinsic pathways)
4. **Fibrinolysis**

# Coagulation: Formation of fibrin meshwork (Threads) to form a CLOT



# Clotting Factors

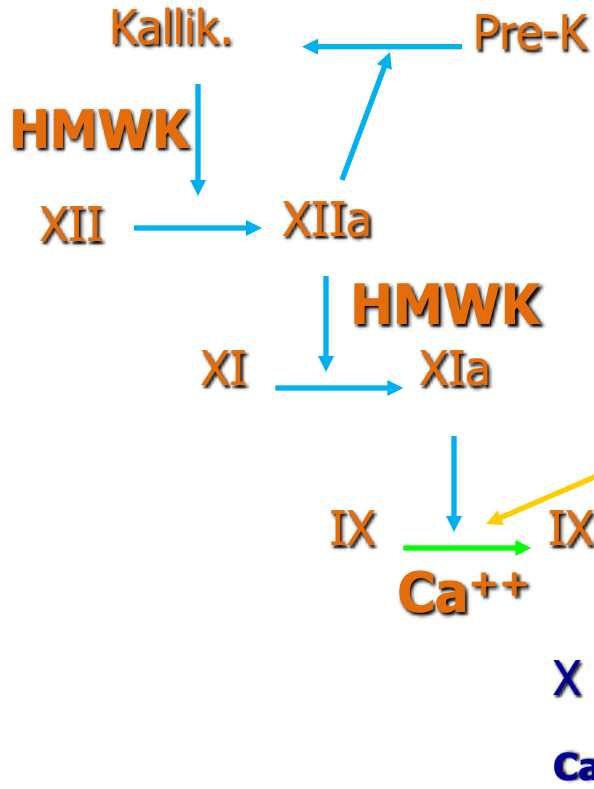
Factors	Names
I	Fibrinogen
II	Prothrombin
III	Thromboplastin (tissue factor)
IV	Calcium
V	Labile factor
VII	Stable factor
VIII	Antihemophilic factor
IX	Antihemophilic factor B
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hageman factor
XIII	Fibrin stabilizing factors

- **Prothrombin (factor II):**
  - is a plasma protein,  $\alpha_2$ -globulin
  - present in normal plasma in a concentration of 15 mg/dl
  - it is unstable protein that can be split easily into **thrombin**
  - it is continually formed by the liver
- **Vitamin K is important for normal production of prothrombin by the liver.**
- Lack of vit K or liver disease can decrease the of prothrombin formation to a very low level >>>> bleeding
- **Thrombin:**
  - is a protein enzyme with weak proteolytic capabilities
  - it acts on fibrinogen to form one molecule of *fibrin monomer*
  - *fibrin monomers* polymerize with one another to form fibrin fibers
  - it activates factor XIII

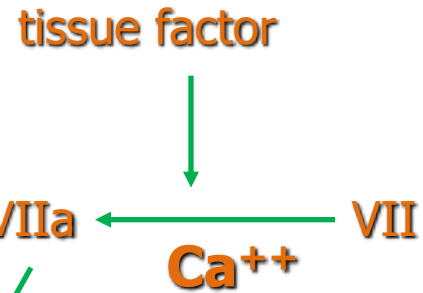


- **Fibrin-stabilizing factor (XIII):**
  - is a plasma protein
  - it is also released from platelets that is entrapped in the clot
  - it must be activated before it affects the fibrin fibers
  - activated XIII factor operates as an enzyme causing additional strength of fibrin meshwork
- **Fibrinogen (factor I):**
  - is a high-molecular-weight plasma protein
  - it is continually formed by the liver
  - little or no fibrinogen leak from blood vessels
- **Blood Clot:**
  - is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, plasma.

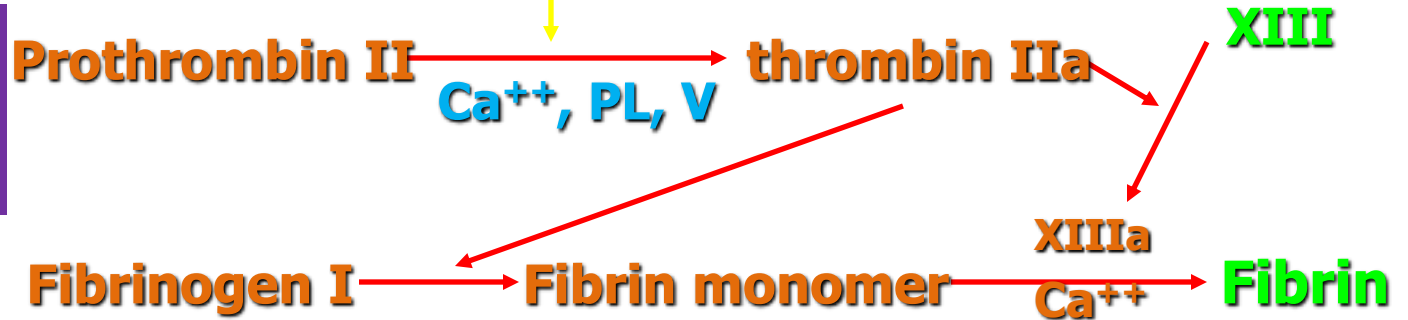
# Intrinsic system



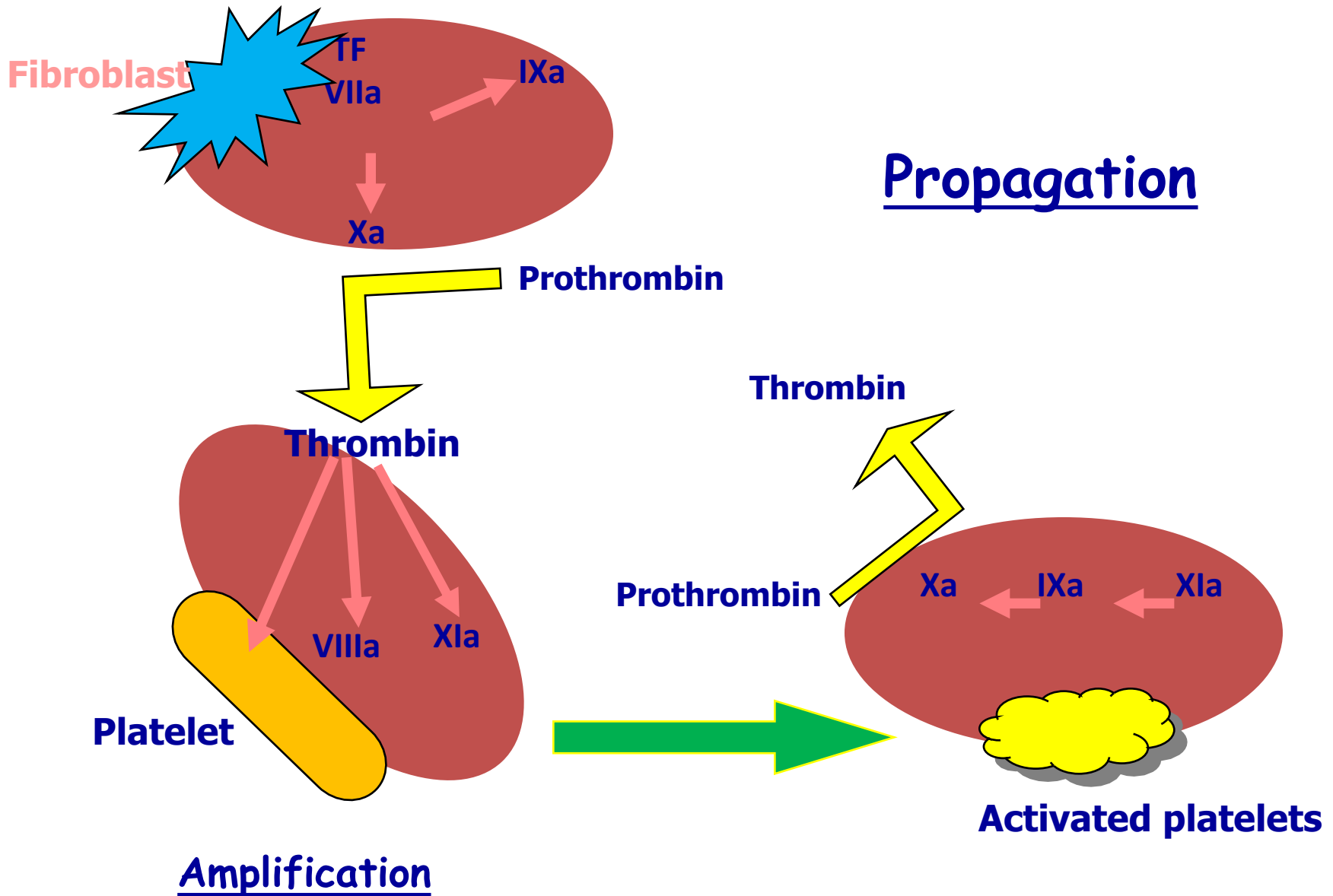
# Extrinsic system



**Final common pathway**



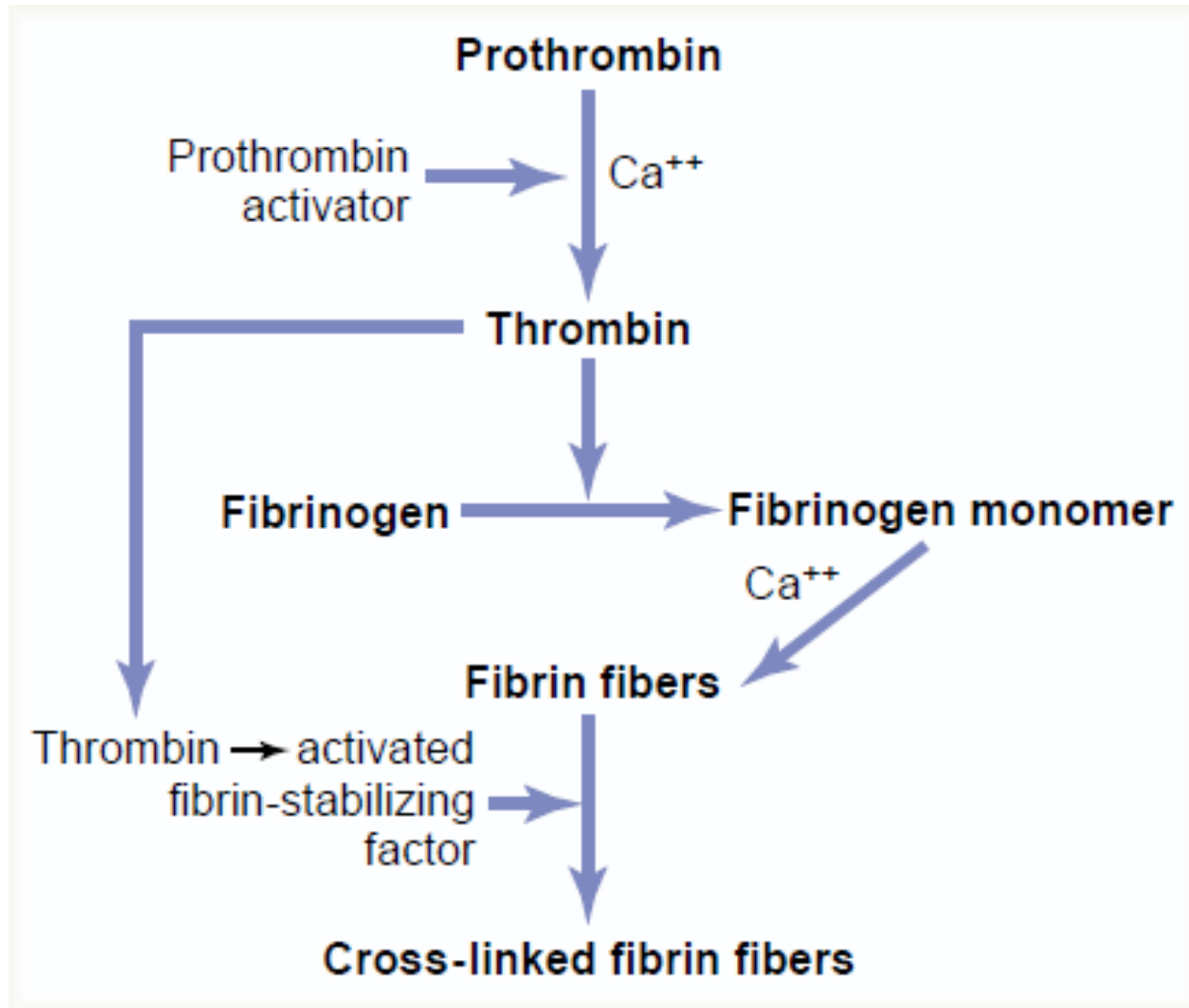
# Cell based model



# Thrombin

- Thrombin changes fibrinogen to fibrin
- Thrombin is essential in platelet morphological changes to form primary plug
- Thrombin stimulates platelets to release ADP & thromboxane A<sub>2</sub>; both stimulate further platelets aggregation
- Activates factor V

# ACTION OF **THROMBIN** ON FIBRINOGEN TO FORM FIBRIN



# Blood coagulation

## (clot formation)

- A series of biochemical reactions leading to the formation of a blood clot within few seconds after injury
- Prothrombin (inactive thrombin) is activated by a long intrinsic or short extrinsic pathways
- This reaction leads to the activation of **thrombin** enzyme from inactive form **prothrombin**
- Thrombin will change **fibrinogen** (plasma protein) into **fibrin** (insoluble protein)

# Intrinsic pathway

- The trigger is the activation of **factor XII** by contact with foreign surface, injured blood vessel, and glass.
- Activated factor XII will activate factor **XI**
- Activated factor XI will activate **IX**
- Activated factor **IX + factor VIII + platelet phospholipid factor (PF<sub>3</sub>) + Ca** activate factor **X**
- Following this step the pathway is **common** for both intrinsic and extrinsic

# Extrinsic pathway

- Triggered by material released from damaged tissues (**tissue thromboplastin**)
- Tissue thromboplastin + VII + Ca → activate X

## Common pathway

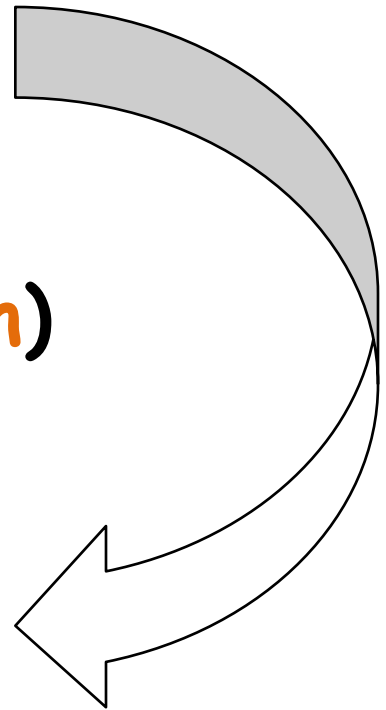
- Activated factor X + factor V + PF3 + Ca activate **prothrombin activator**; a proteolytic enzyme which activates **prothrombin**.
- **Activated prothrombin** activates thrombin
- Thrombin acts on fibrinogen and change it into insoluble thread like fibrin.
- Factor XIII + Calcium → strong fibrin (strong clot)



# Activation of Blood Coagulation

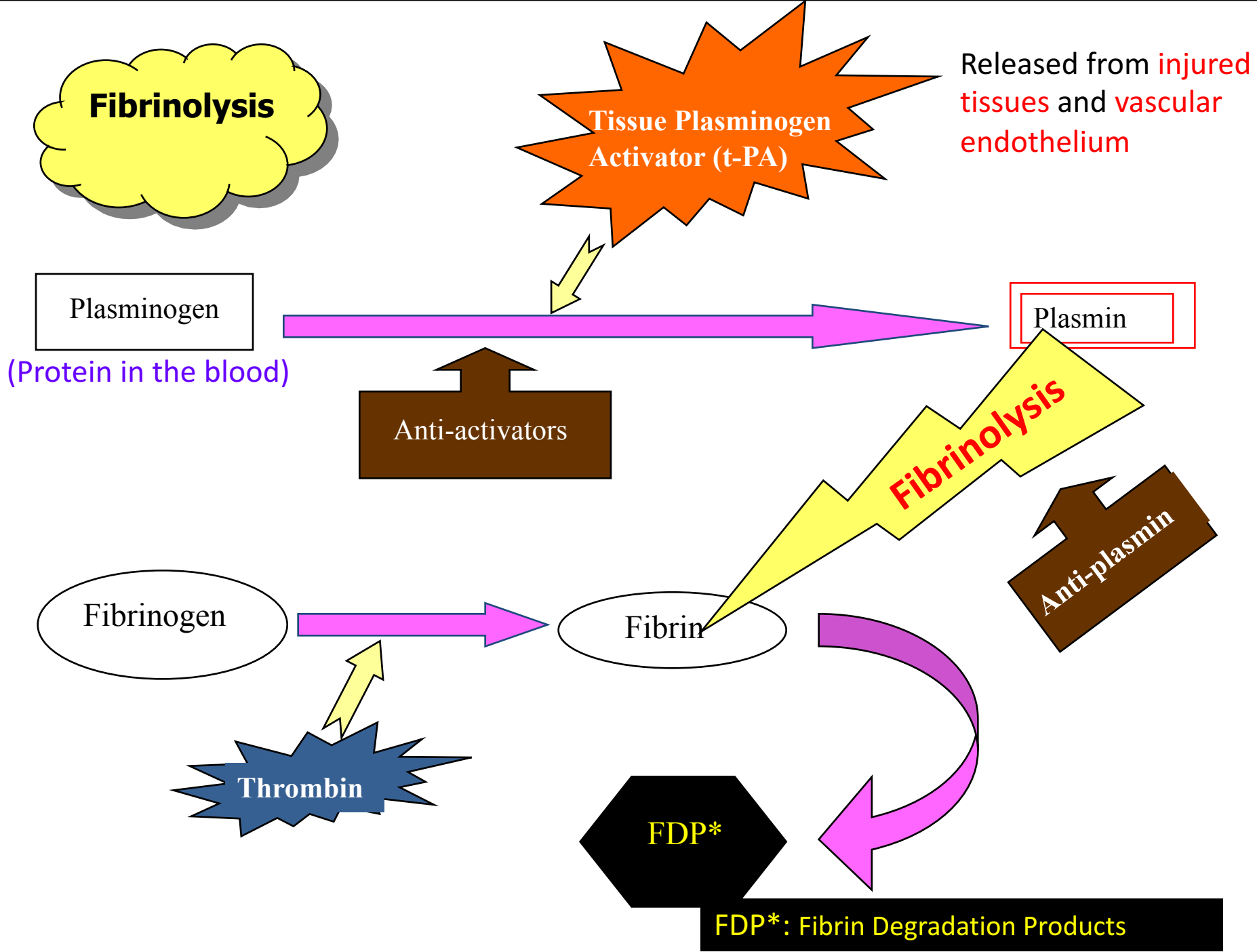
- **Intrinsic Pathway:** all clotting factors present in the blood
- **Extrinsic Pathway:** triggered by tissue factor (**thromboplastin**)

**Common Pathway**



# Fibrinolysis

- Formed blood clot can either become fibrous or dissolved.
- Fibrinolysis (dissolving) = Break down of fibrin by naturally occurring enzyme **plasmin** therefore prevent intravascular blocking.
- There is a *balance* between clotting and fibrinolysis
  - **Excess clotting** → **blocking of Blood Vessels**
  - **Excess fibrinolysis** → **tendency for bleeding**



# Plasmin

- Is present in the blood in an inactive form plasminogen
- Is activated by tissue plasminogen activators (t-PA) in blood.
- Digests intra & extra vascular deposit of Fibrin → fibrin degradation products (FDP)
- Unwanted effect of plasmin is the digestion of clotting factors

# Plasmin

- **Plasmin** is controlled by:
  - Tissue Plasminogen Activator Inhibitor (TPAI)
  - Antiplasmin from the liver
- **Uses:**
  - Tissue Plasminogen Activator (TPA) used to activate plasminogen to dissolve coronary clots

# Prevention of blood clotting in the normal vascular system and Anticoagulants

- **Endothelial surface factors**
  - Smoothness of the ECS.
  - Glycocalyx layer
  - Thrombomodulin protein
- **Fibrin fibers**, adsorbs ~ 90% of thrombin to removes it from circulating blood
- **Antithrombin III**, combines the remaining thrombin and removes it from blood
- **Heparin**, combines with Antithrombin III and quickly removes thrombin from blood
  - Liver, lungs, mast cells, basophils

# Conditions that cause excessive bleeding

- Vitamin K Deficiency
  - Prothrombin, Factor VII, Factor IX, Factor X require vitamin K for their synthesis
  - Hepatitis, Cirrhosis, acute yellow atrophy AND GI disease
- Hemophilia
  - ↑ bleeding tendency.
  - X-linked disease.
  - Affects males.
  - 85% due to Factor VIII deficiency (hemophilia A), and 15% due to Factor IX deficiency (hemophilia B).
- Thrombocytopenia
  - Very low number of platelets in blood (< 50,000/ $\mu$ l)
  - *Thrombocytopenia purpura*, hemorrhages throughout all the body tissues
  - *Idiopathic Thrombocytopenia*, unknown cause.