Coagulation Mechanisms

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Objectives

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

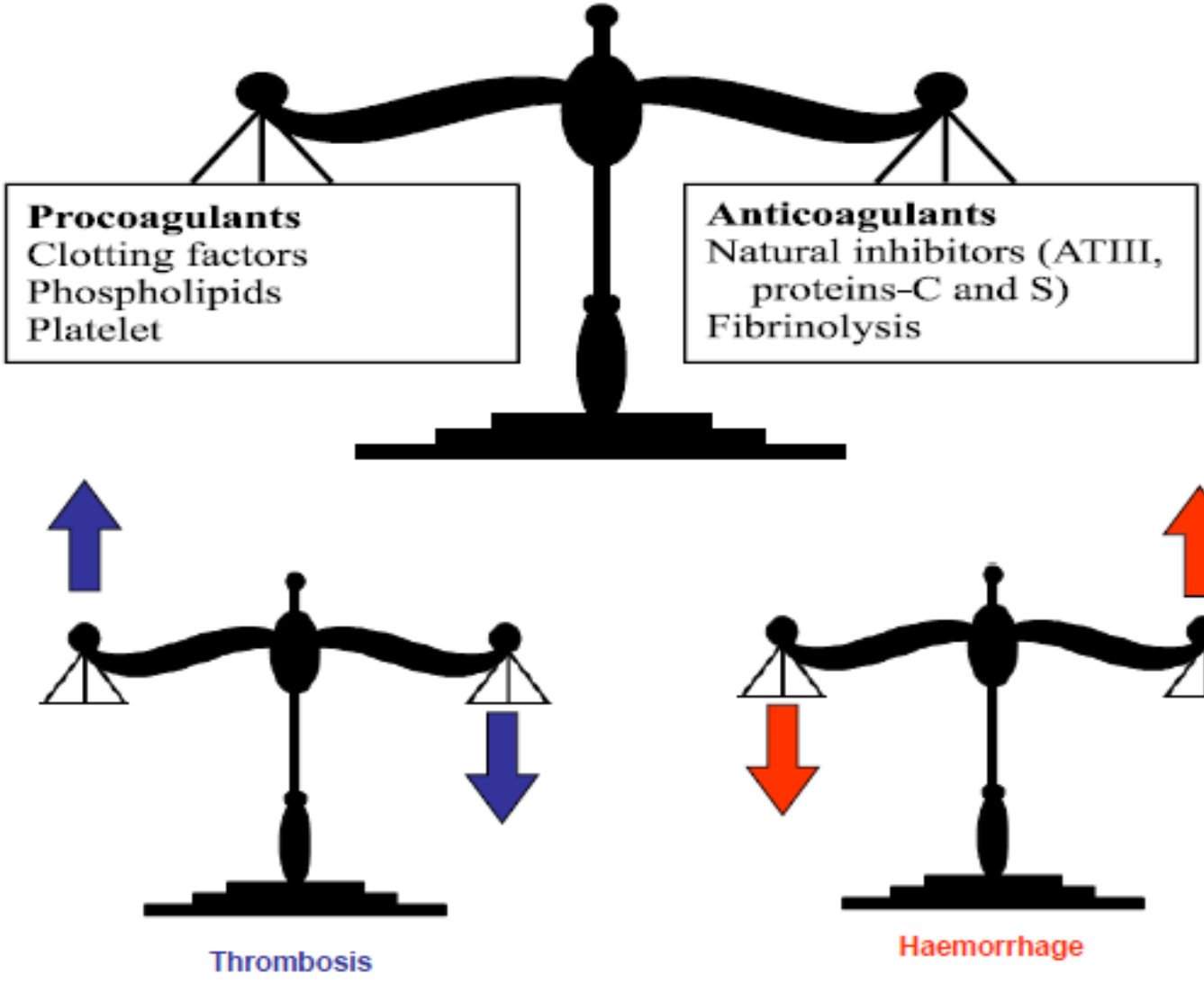
1. Recognize the different clotting factors.
2. Understand the role of calcium ions during clotting cascades.
3. Describe the cascades of intrinsic and extrinsic pathways for clotting.
4. Recognize process of fibrinolysis and function of plasmin.
5. Recognize some conditions causing excessive bleeding.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

Mechanism of Blood Coagulation

- **A crucial physiological *balance* exists between factors promoting coagulation (procoagulants) & factors inhibiting coagulation (anticoagulants).**

- **Blood Coagulation depends on the *balance* between these two factors.**

- **Disturbances in this *balance* could lead to thrombosis OR bleeding.**


Procoagulants
Clotting factors
Phospholipids
Platelet
Anticoagulants
Natural inhibitors (ATIII, proteins-C and S)
Fibrinolysis
Thrombosis
Haemorrhage

Hemostasis:

prevention or stoppage of blood loss.

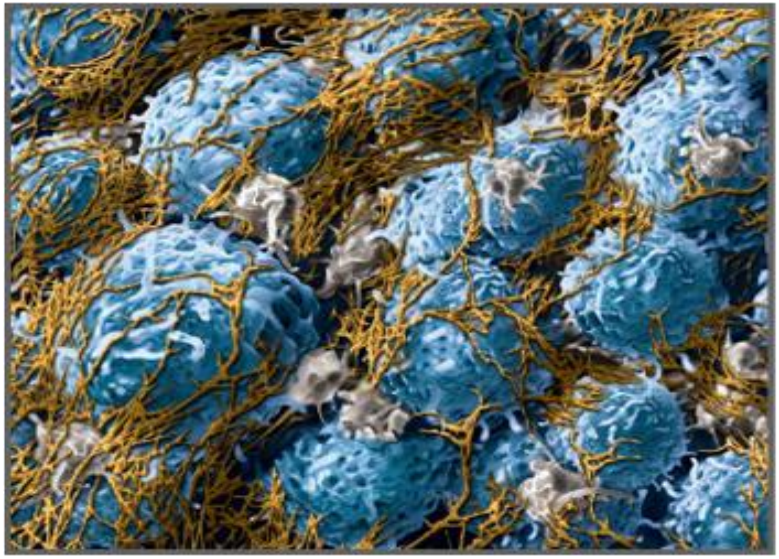
Hemostatic Mechanisms:

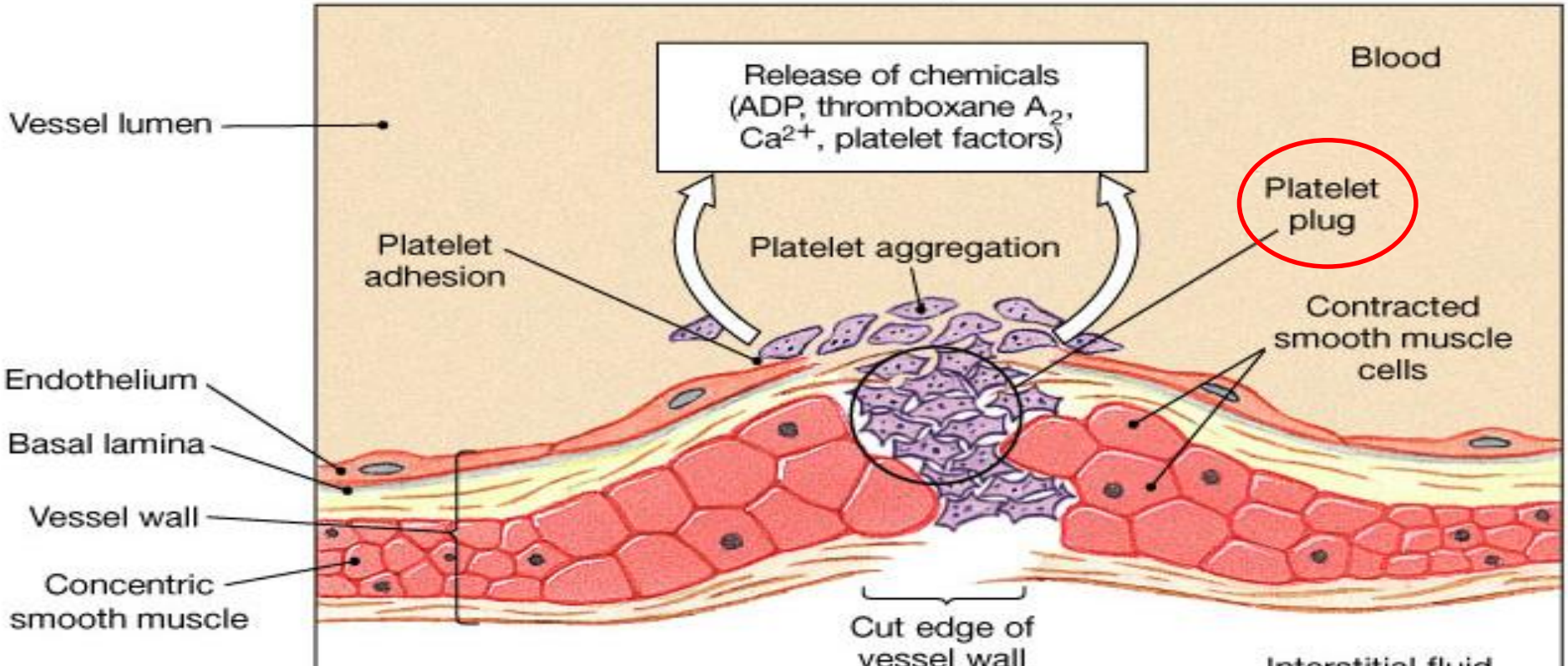
1. **Vessel wall** (Vasoconstriction)
2. **Platelets** (Production and activation, Platelets Plug formation)
3. **Blood coagulation**

   Clot formation (intrinsic & extrinsic pathways)
4. **Fibrinolysis**

Coagulation:

Formation of fibrin meshwork (threads) to form a blood CLOT.





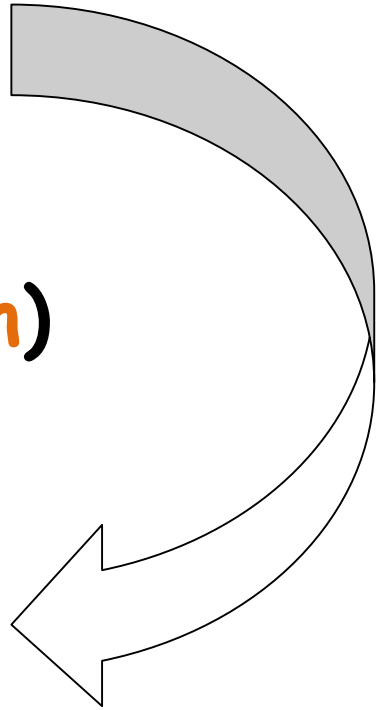
Blood coagulation
(clot formation)

- 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)

Activation of Blood Coagulation

- **Intrinsic Pathway:** all clotting factors present in the blood

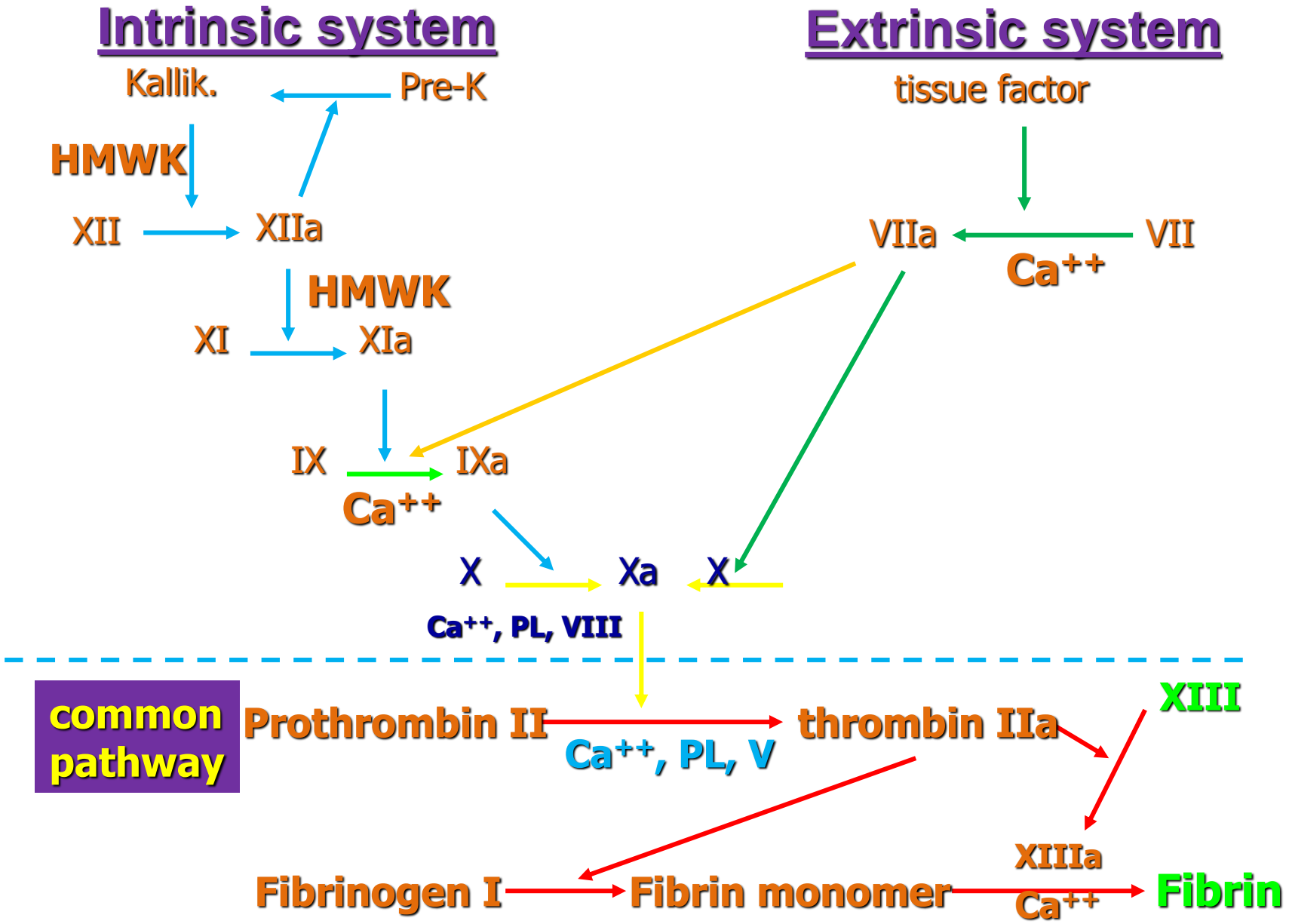
- **Extrinsic Pathway:** triggered by tissue factor (thromboplastin)



Common Pathway

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 stablizing factors


Intrinsic system
Kallik.
Pre-K
HMWK
XII
XIIa
HMWK
XI
XIa
IX
IXa
Ca++
X
Xa
Ca++, PL, VIII
Extrinsic system
tissue factor
VIIa
VII
Ca++
X
common pathway
Prothrombin II
Ca++, PL, V
thrombin IIa
XIII
XIIIa
Ca++
Fibrinogen I
Fibrin monomer
Fibrin

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 Xl will activate IX.

- Activated factor IX + factor VIII + platelet phospholipid factor (PF3)+ Ca ions activate factor X.

- Following this step the pathway is common for both intrinsic and extrinsic

Extrinsic pathway

- Triggered by material released from damaged tissues TF (tissue factor-tissue thromboplastin).
-
- Tissue thromboplastin + VII + Caions → activate X

Common pathway

- Activated factor X + factor V +PF3 + Ca ions 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)

- **Prothrombin (factor II):**

- unstable protein that can be split easily into thrombin.
- it's a plasma protein formed by the liver

- Vitamin K is important for normal production of prothrombin by the liver.

- Lack of vitamin K or liver diseases can decrease prothrombin formation (and other Vitamin K dependent factor VII,IX & X) and can lead to bleeding.

- **Thrombin:**

- proteolytic enzyme, that breaks down fibrinogen into fibrin *monomers.*
- *fibrin monomers* polymerize with one another to form fibrin fibres.

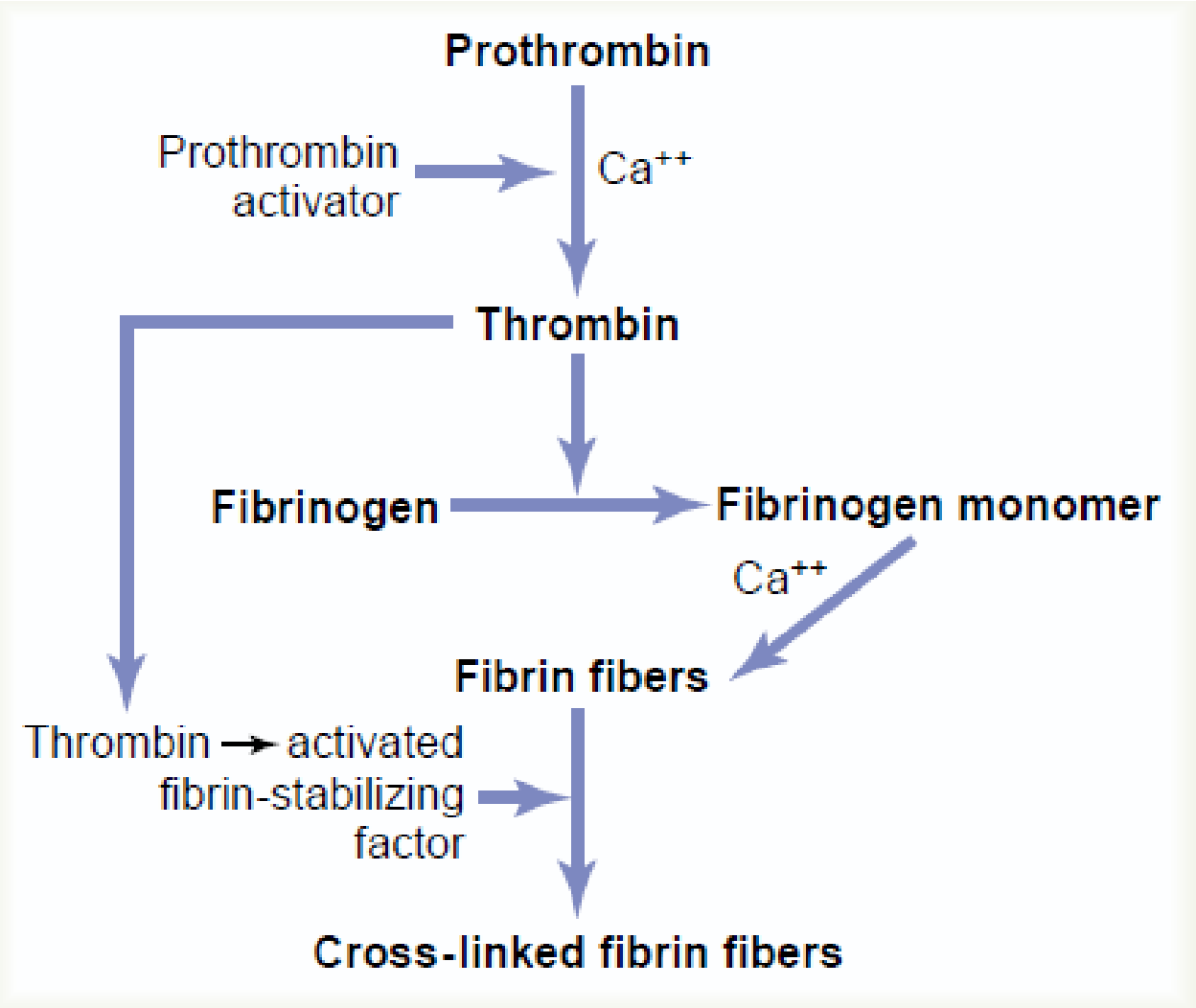
- **Other actions of thrombin:**

- **activates factors V, VIII, XI, and XIII.**
- **activates platelets.**
- **Bound to thrombomodulin activates the anticoagulant Protein C.**

Thrombin

- Thrombin changes fibrinogen to fibrin.
- Thrombin is essential in platelet morphological changes to form primary plug.
- Thrombin stimulates platelets to release ADP & thromboxane A2; both stimulate further platelets aggregation.
- Activates factor V, VIII & XIII.

ACTION OF THROMBIN ON FIBRONOGEN TO FORM FIBRIN

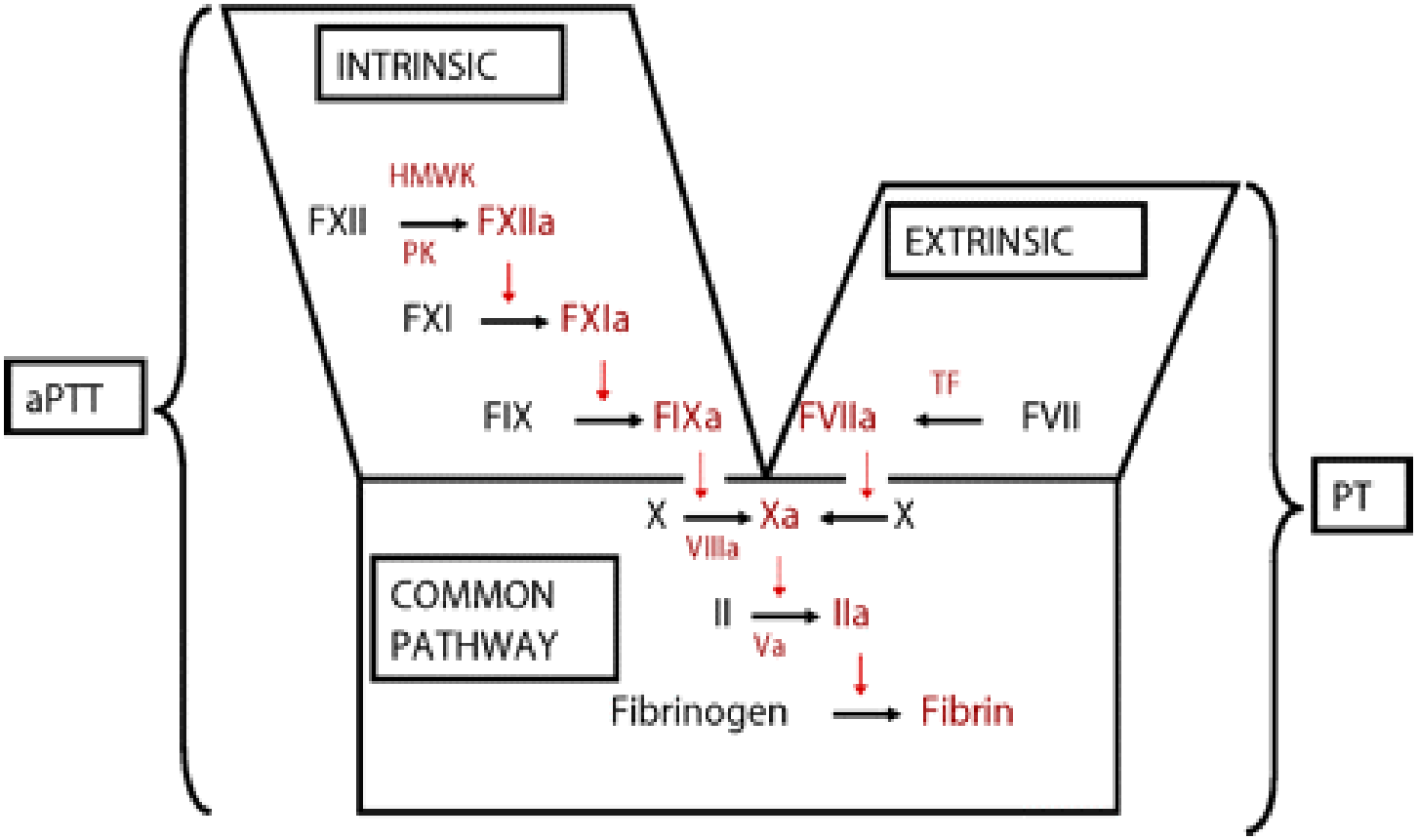


- **Fibrin-stabilizing factor (XIII):**

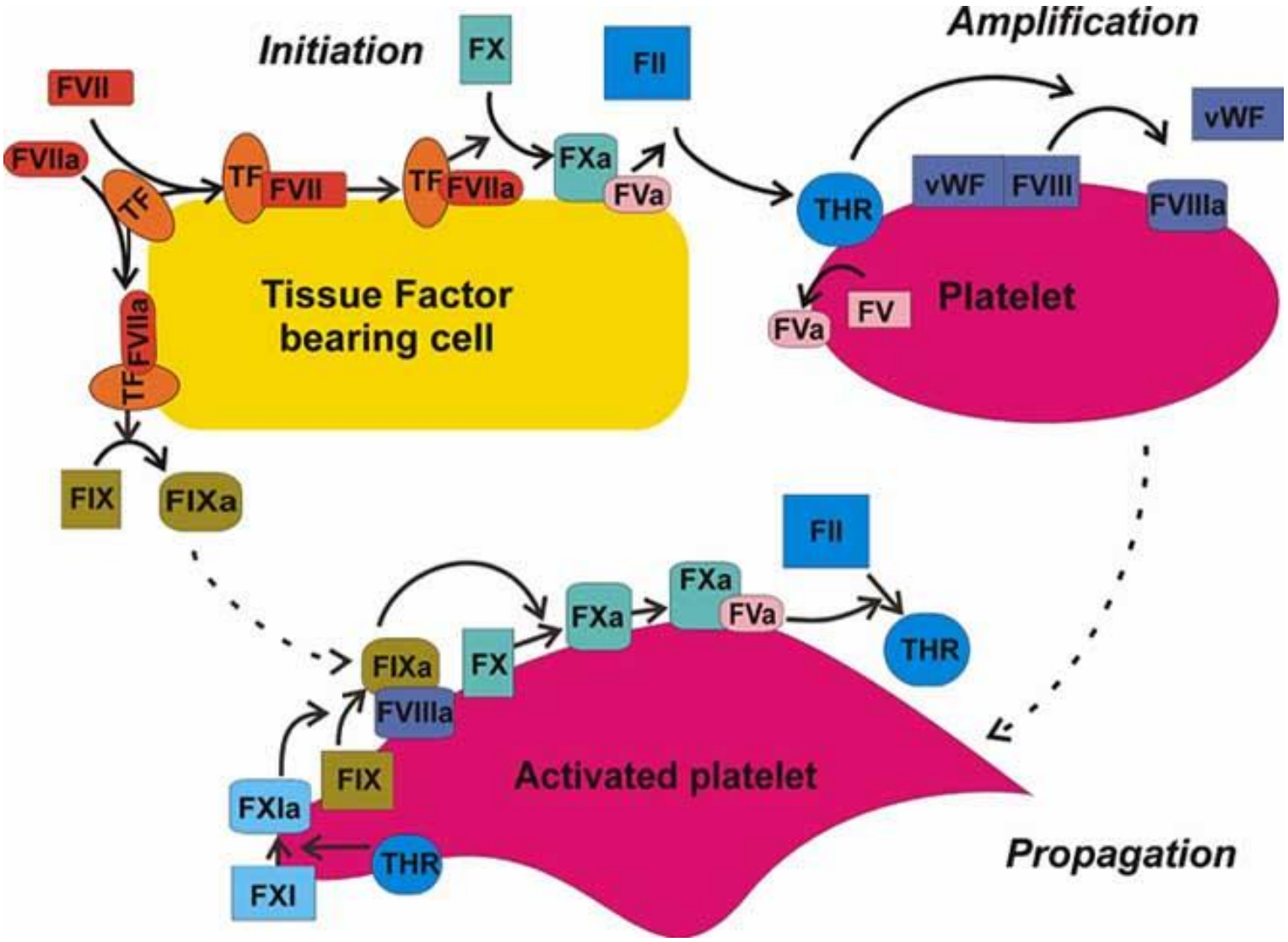
- it must be activated before it affects the fibrin fibres
  - activated XIII factor operates as an enzyme causing additional strength of fibrin meshwork.

- **Fibrinogen (factor I):**
  - is a high-molecular-weight plasma protein.
  - formed by the liver.
  - little or no fibrinogen leads to leak from blood vessels.

Coagulation Factor Activation

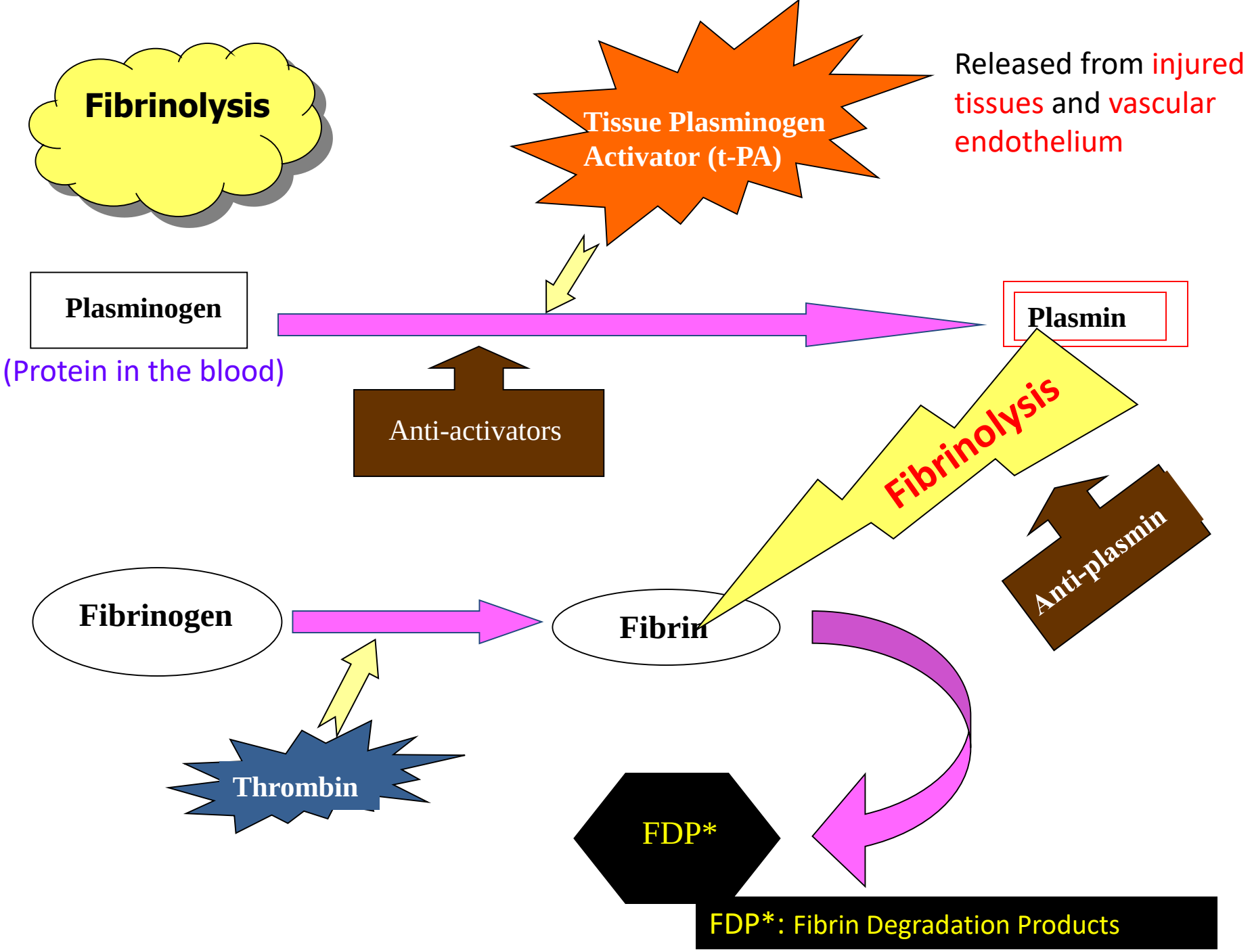


CELL BASED MODEL



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


Fibrinolysis
Tissue Plasminogen Activator (t-PA)
Released from injured tissues and vascular endothelium
Plasminogen
(Protein in the blood)
Plasmin
Anti-activators
Fibrinolysis
Anti-plasmin
Fibrinogen
Fibrin
Thrombin
FDP*
FDP*: Fibrin Degradation Products

Plasmin

- present in the blood in an inactive form plasminogen.
- 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.

✓Are u a member of the t-PA team?!

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/µl)
  - ***Thrombocytopenia purpura***, hemorrhages throughout all the body tissues
  - ***Idiopathic Thrombocytopenia,*** unknown cause.