Coagulation Mechanisms

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Objectives

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

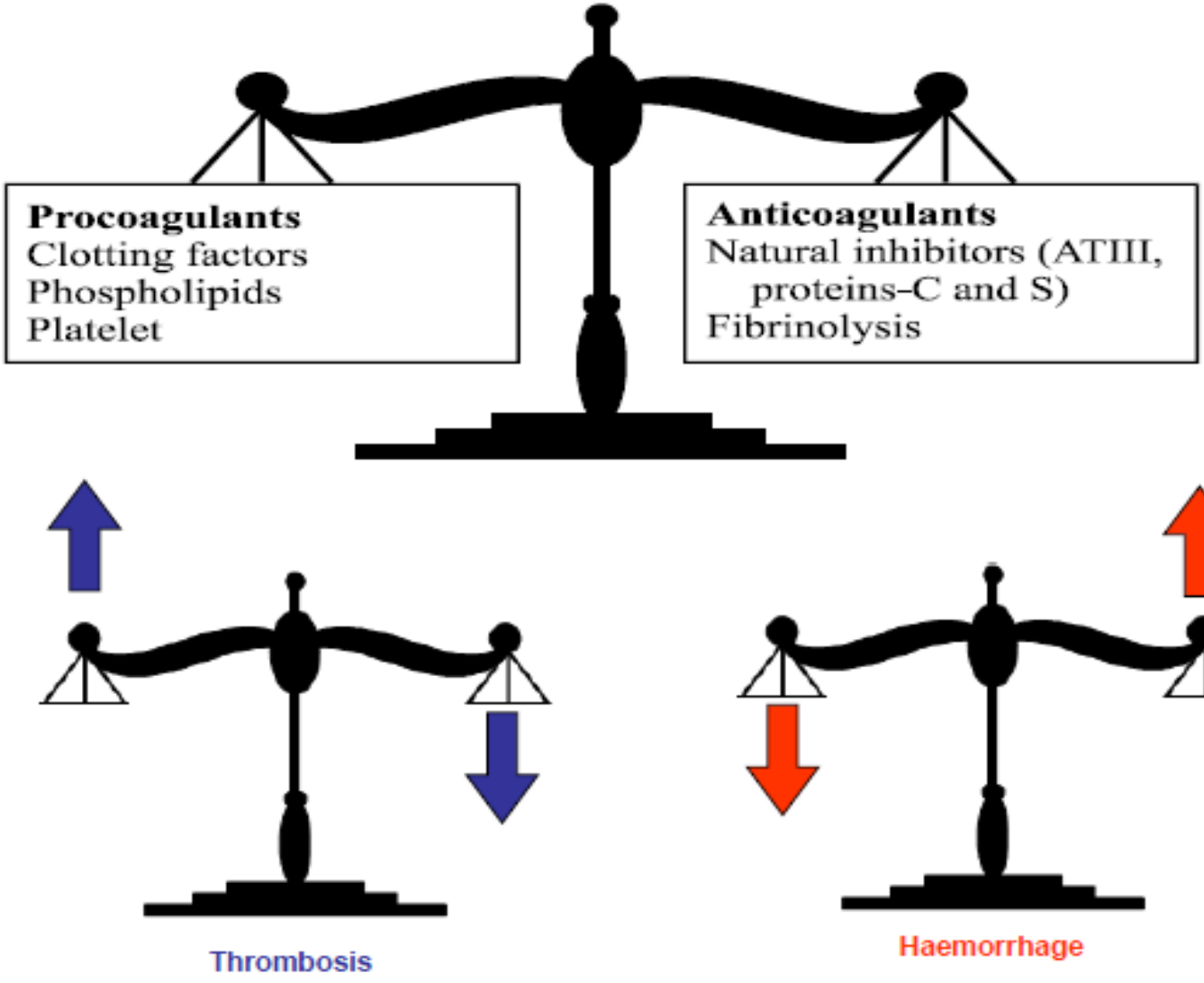
1. Recognize the different clotting factors
2. Understand the role of calcium ions during clotting cascades.
3. Describe the cascades of intrinsic and extrinsic pathways for clotting.
4. Recognize process of fibrinolysis and function of plasmin
5. Recognize some conditions causing excessive bleeding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

Mechanism of Blood Coagulation

- **A crucial physiological *balance* exists between factors promoting coagulation (procoagulants) 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**


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

Hemostasis:

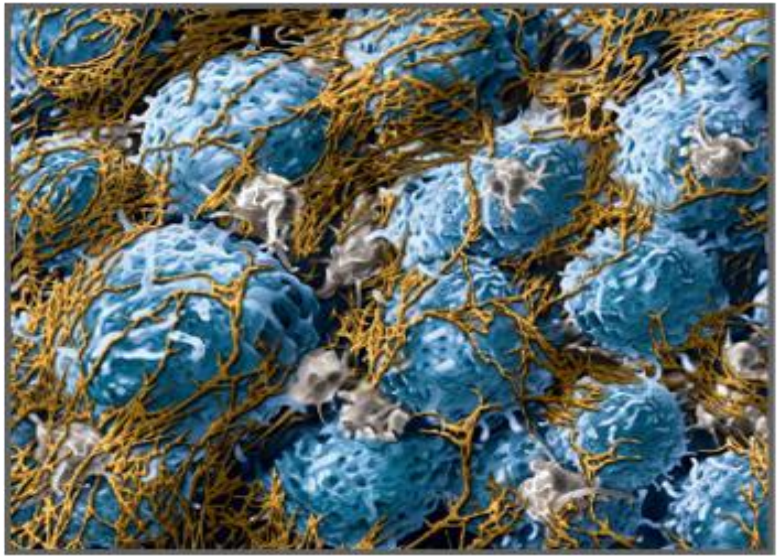
prevention or stoppage of blood loss.

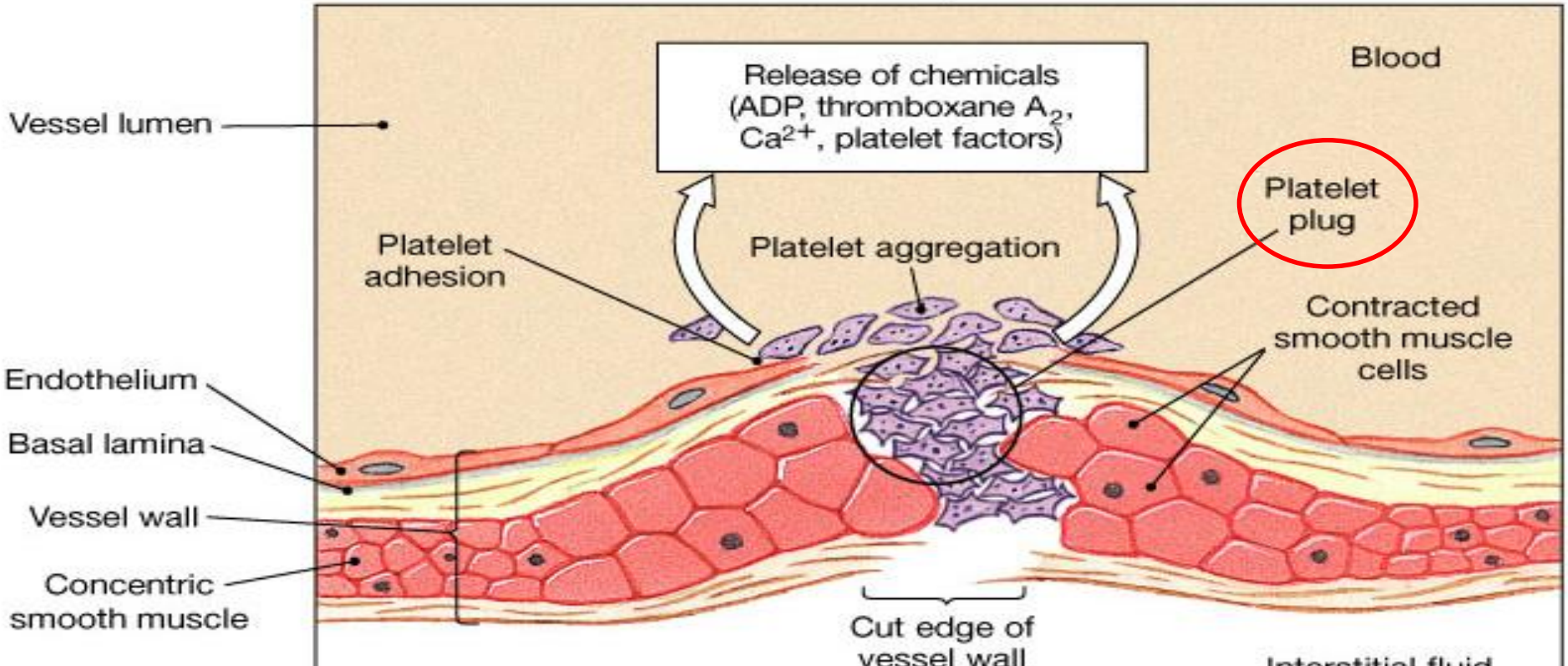
Hemostatic Mechanisms:

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 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 stablizing factors

- **Prothrombin (factor II):**
  - is a plasma protein, a2-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.

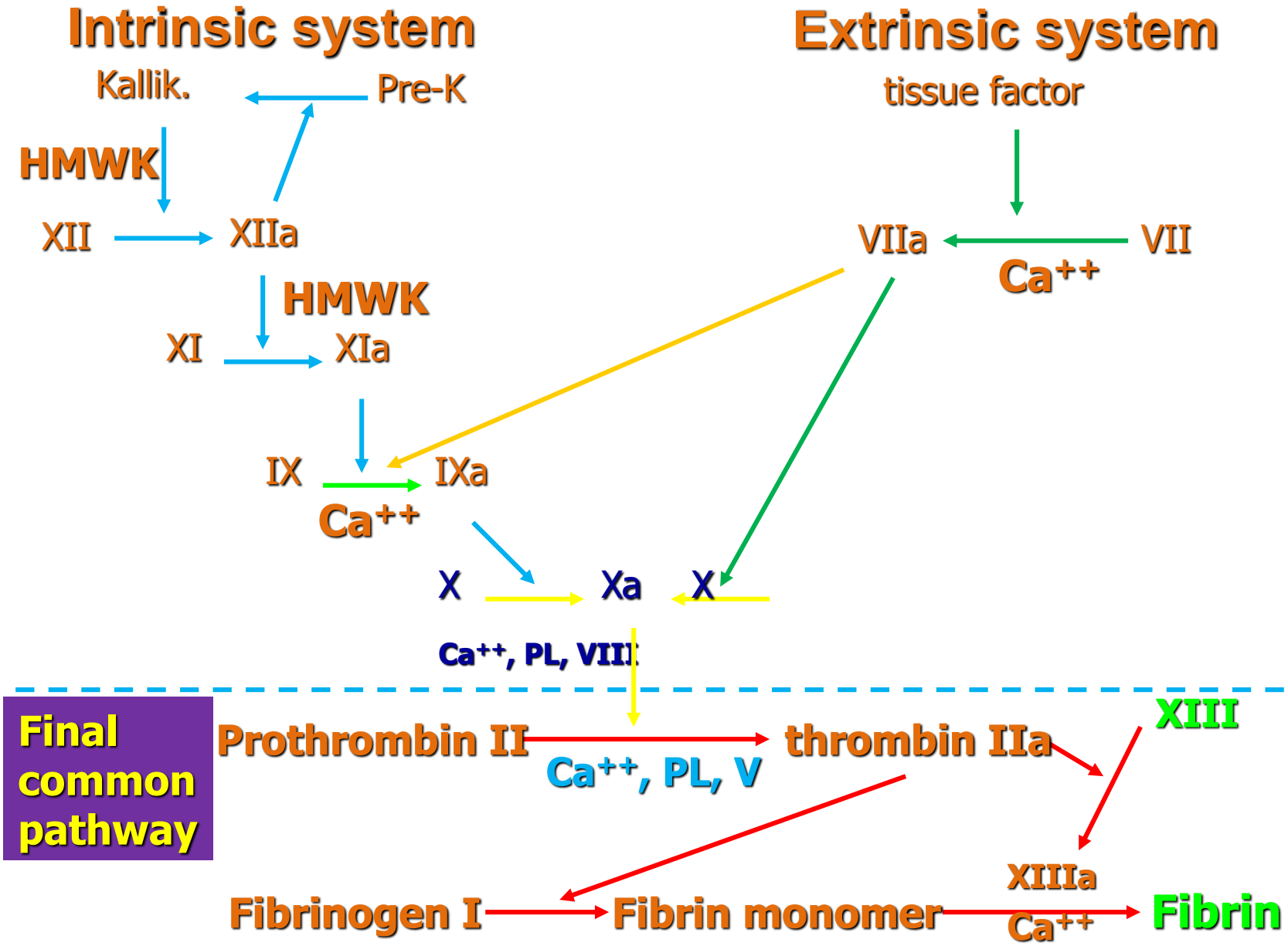
- Lack of vit K or liver disease can decrease the of prothrombin formation to a very low level >>>> bleeding

- **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

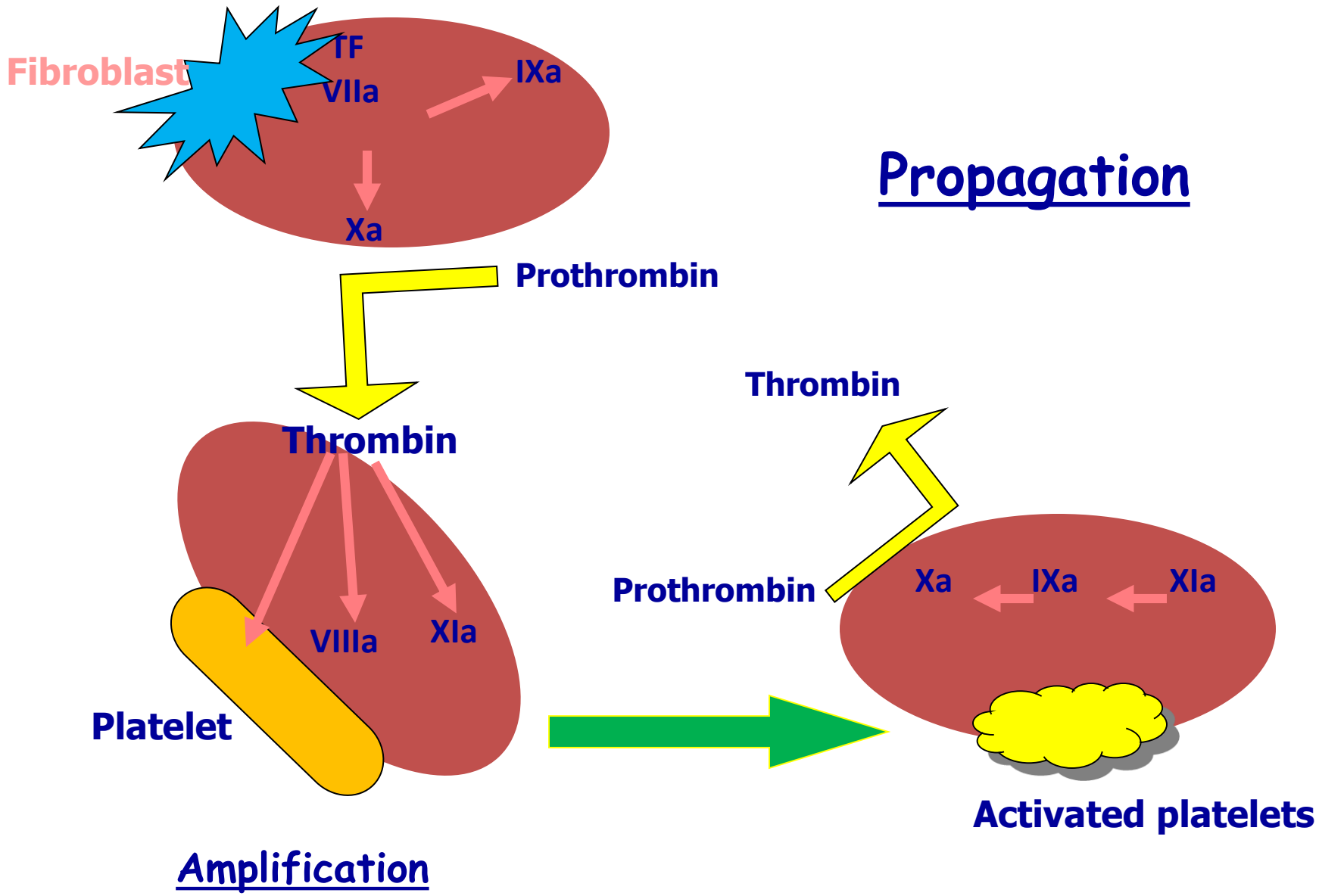
- **Fibrin-stabilizing factor (XIII):**
  - is a plasma protein
  - it is also released from platelets that is entrapped in the clot
  - it must be activated before it affects the fibrin fibers
  - activated XIII factor operates as an enzyme causing additional strength of fibrin meshwork

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

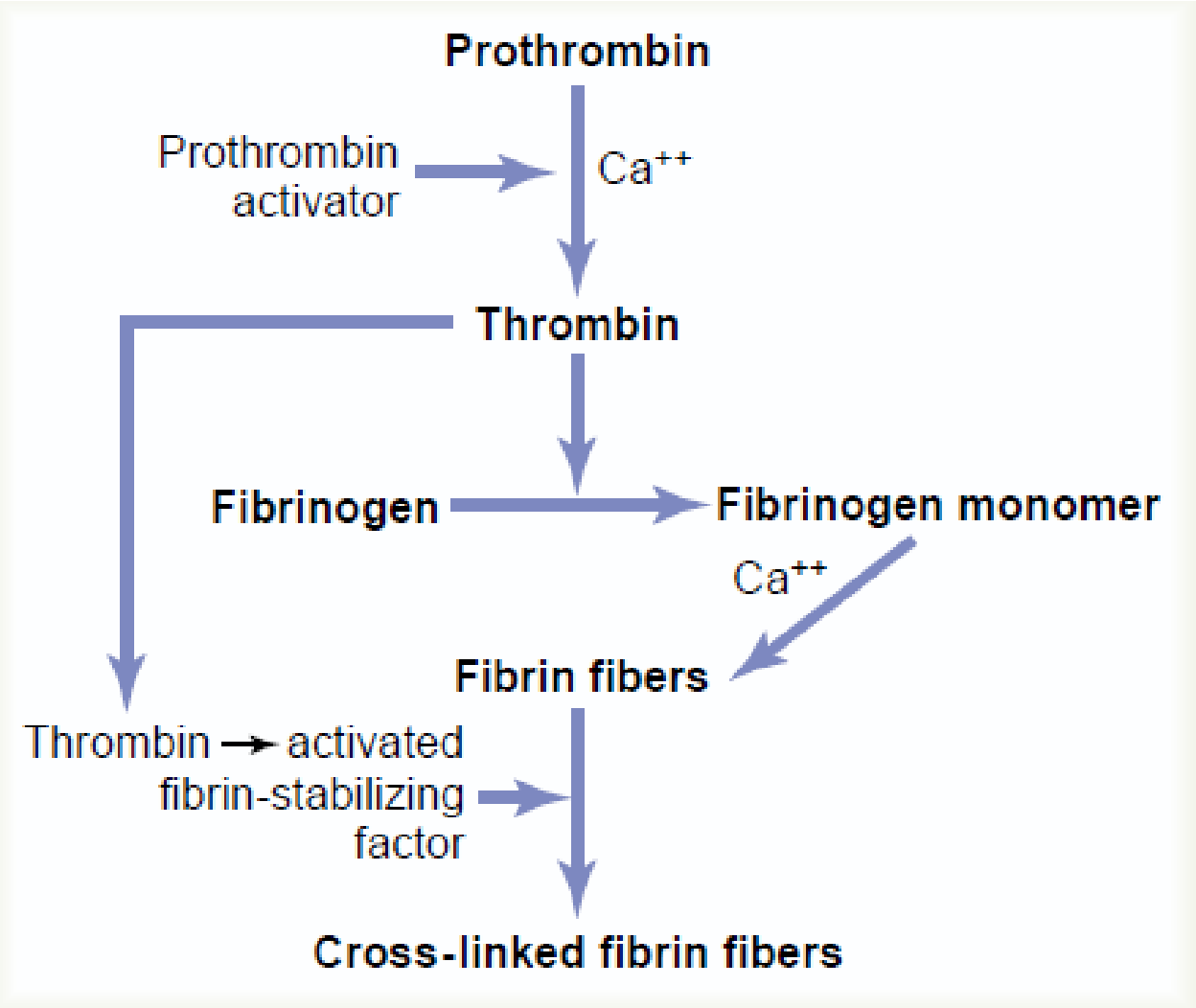
Cell based model



Thrombin

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

ACTION OF THROMBIN ON FIBRONOGEN 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 Xl will activate IX
- Activated factor IX + factor VIII + platelet phospholipid factor (PF3)+ 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

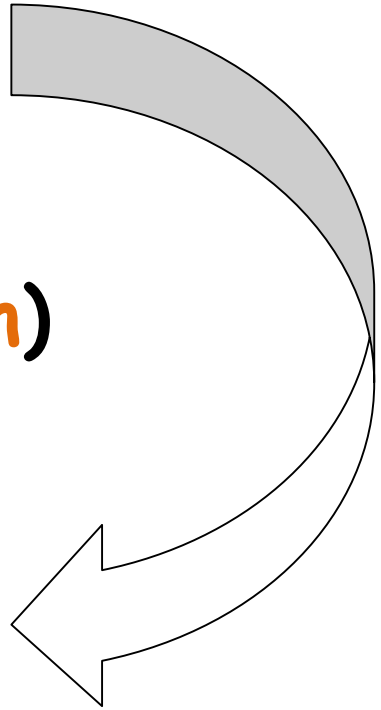
Common pathway

- 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

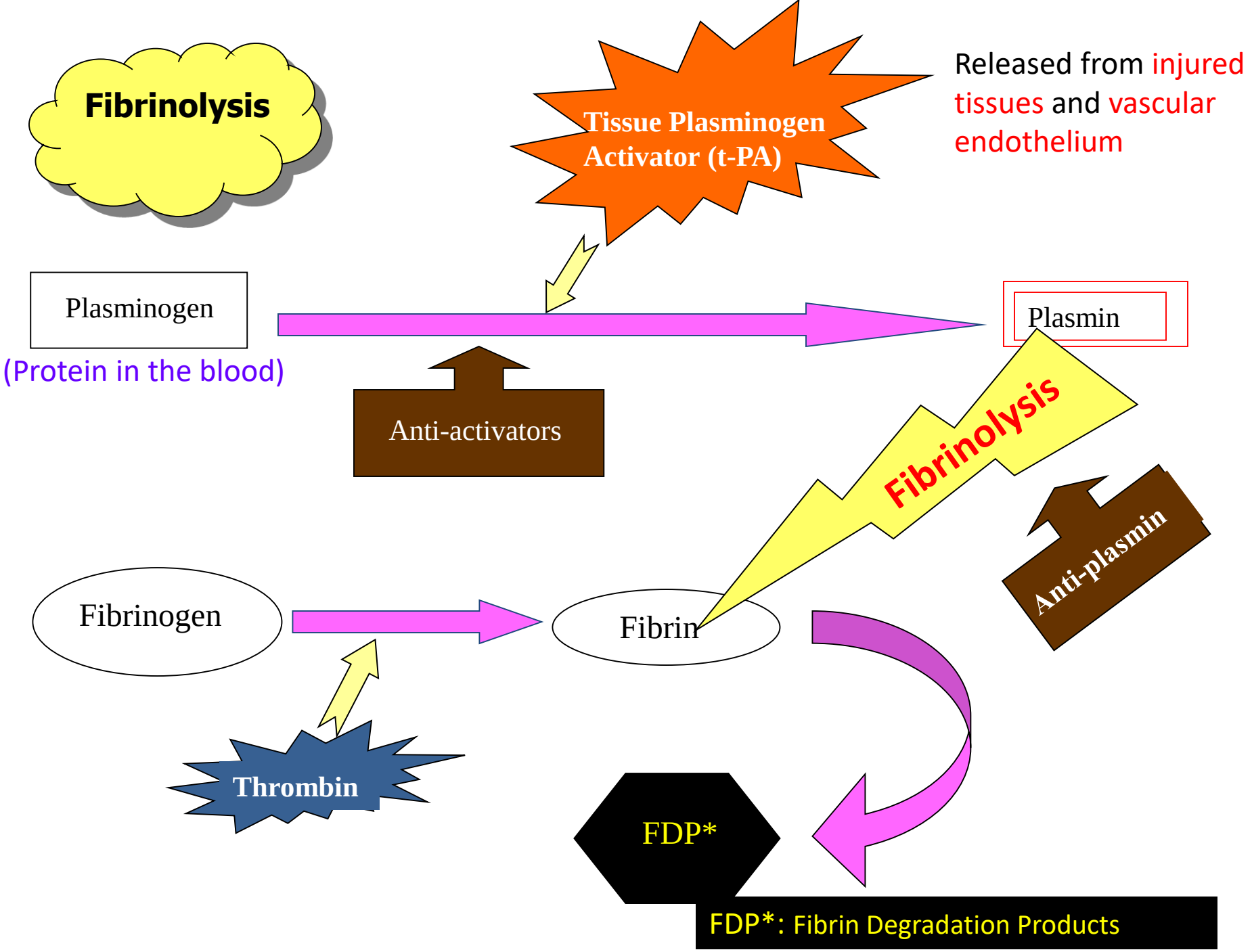
- **Extrinsic Pathway:** triggered by tissue factor (thromboplastin)



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


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

- 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 <u>quickly</u> 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.