Coagulation Mechanisms

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Objectives

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

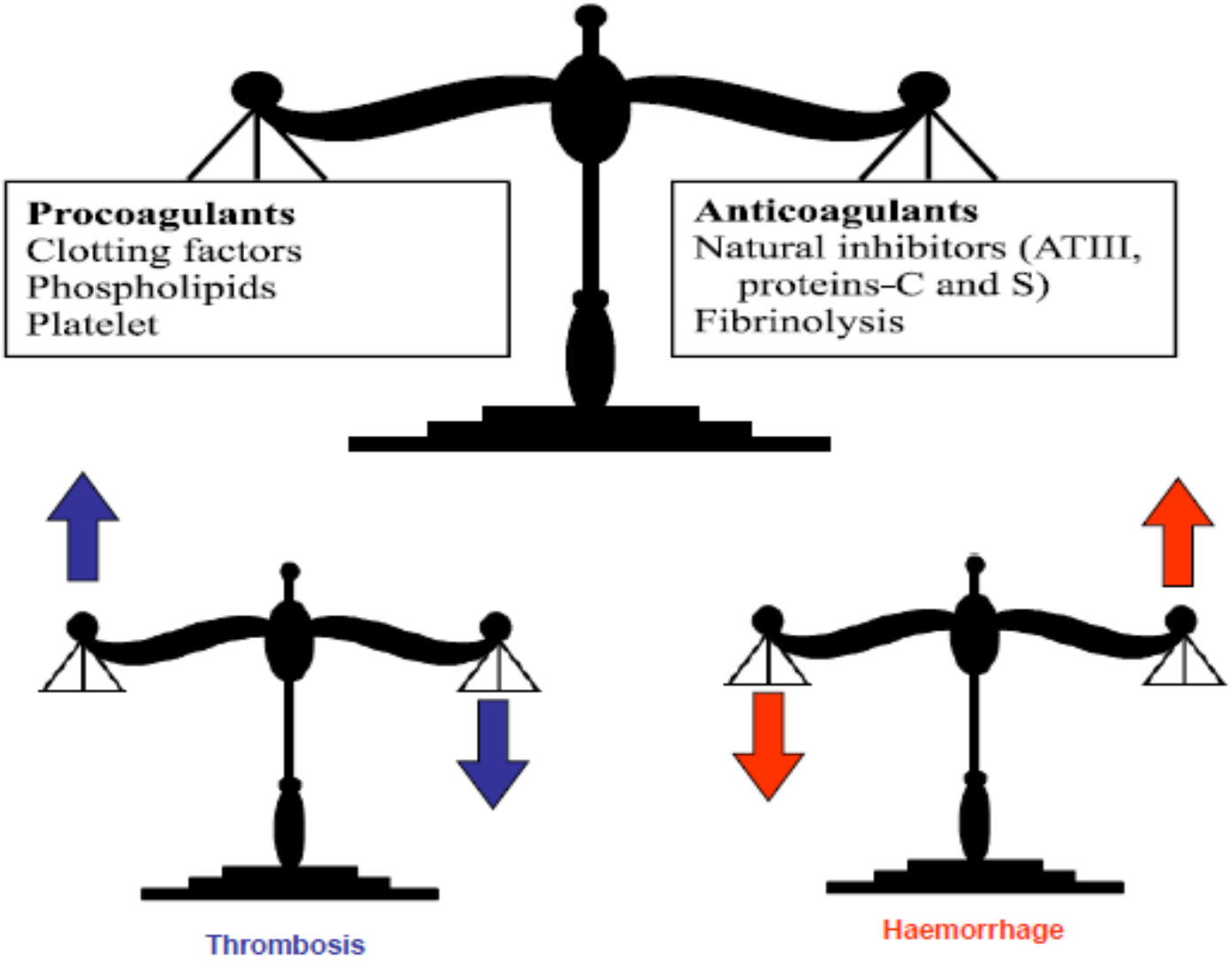
1. Recognize the different clotting factors.
2. Understand the role of calcium ions during clotting cascades.
3. Describe the cascades of intrinsic and extrinsic pathways for clotting.
4. Recognize process of fibrinolysis & function of plasmin.
5. Recognize some conditions causing excessive bleeding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

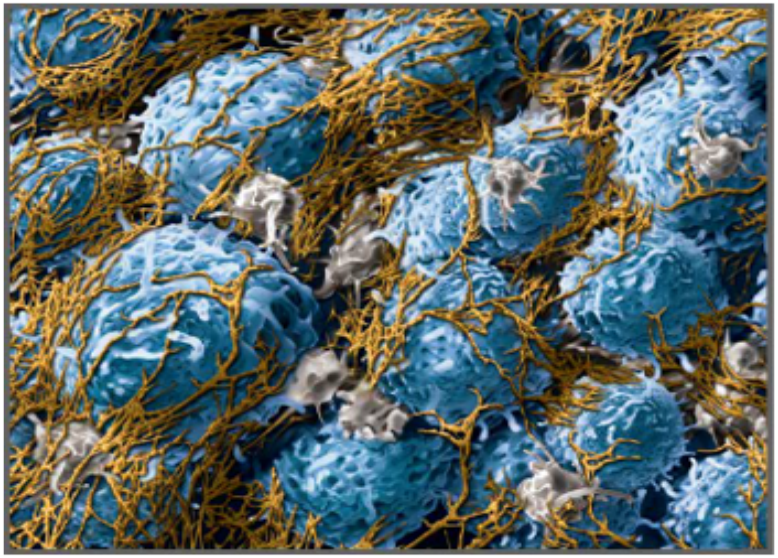
- **Hemostasis:**
  prevention or stoppage of blood loss.

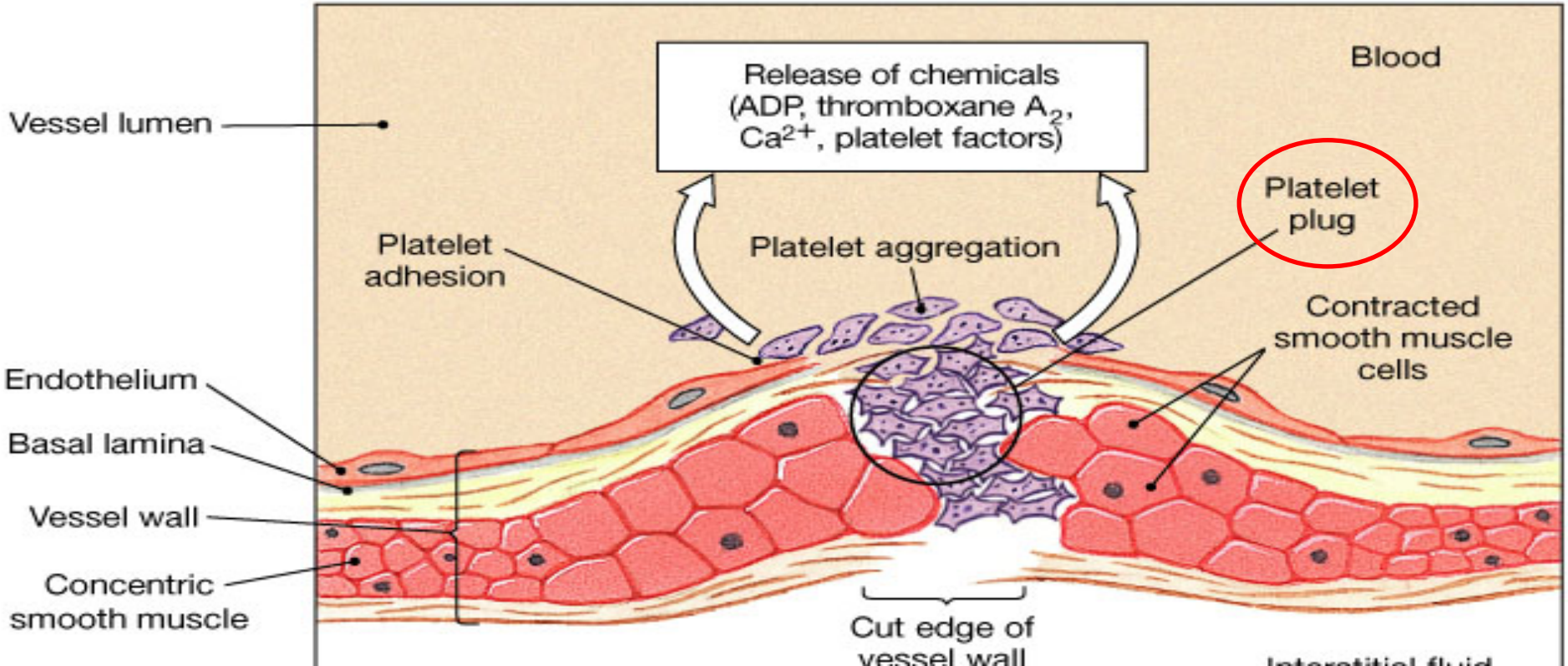
- **Hemostatic Mechanisms:**

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

Coagulation:

Formation of fibrin meshwork (Threads) to form a blood 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):

- plasma protein,continually formed by the liver.

- unstable protein that can be split easily into thrombin.

- Vitamin K is important for normal production of prothrombin by the liver (so as factors ???).

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

➢ Thrombin:

- is a protein enzyme with 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

Procoagulant actions of thrombin enzyme:

1- cleaves fibrinogen into fibrin.

2- Activates clotting factors:
- Xiii to cross link fibrin.
- Intrinsic pathway via factor Xi.
- Cofactor of the activation of factors V & Viii.

3- Stimulates platelet activation.

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

➢ Fibrin-stabilizing factor (XIII):

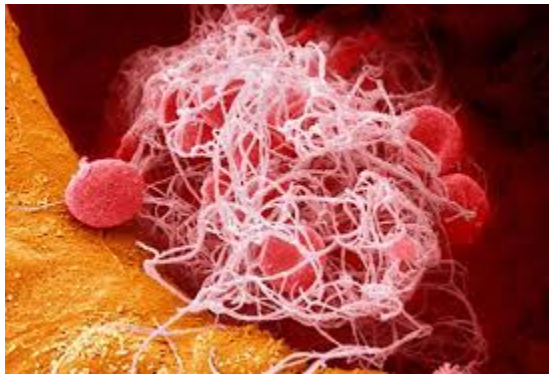
- a plasma protein.
- also released from platelets that is entrapped in the clot.
- it must be activated before it affects the fibrin fibers.
- activated XIII factor operates as an enzyme causing additional strength of fibrin meshwork.

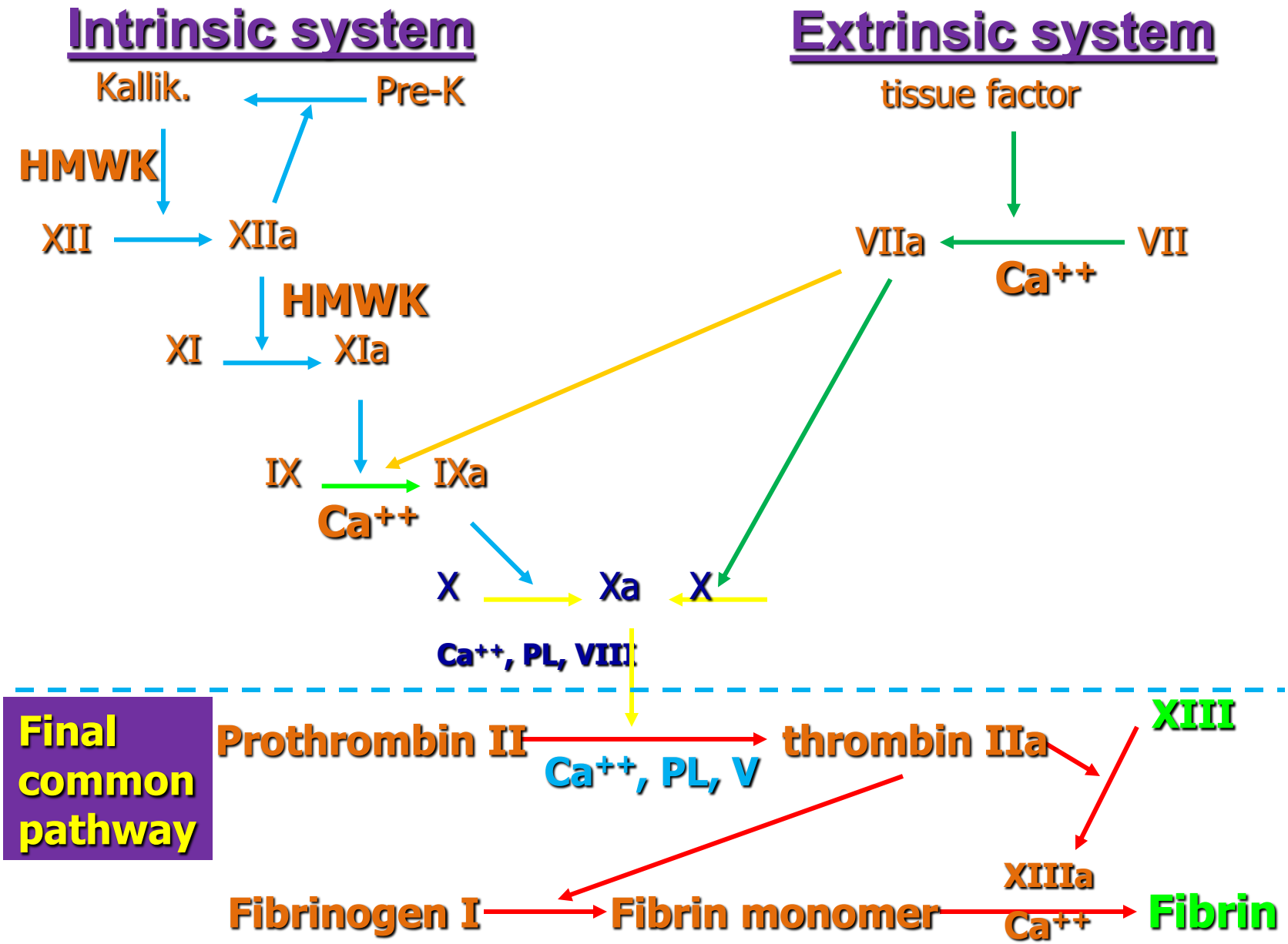
➢ Fibrinogen (factor I):

- is a high-molecular-weight plasma protein
- it is continually formed by the liver
- little or no fibrinogen leads to blood leak from vessels

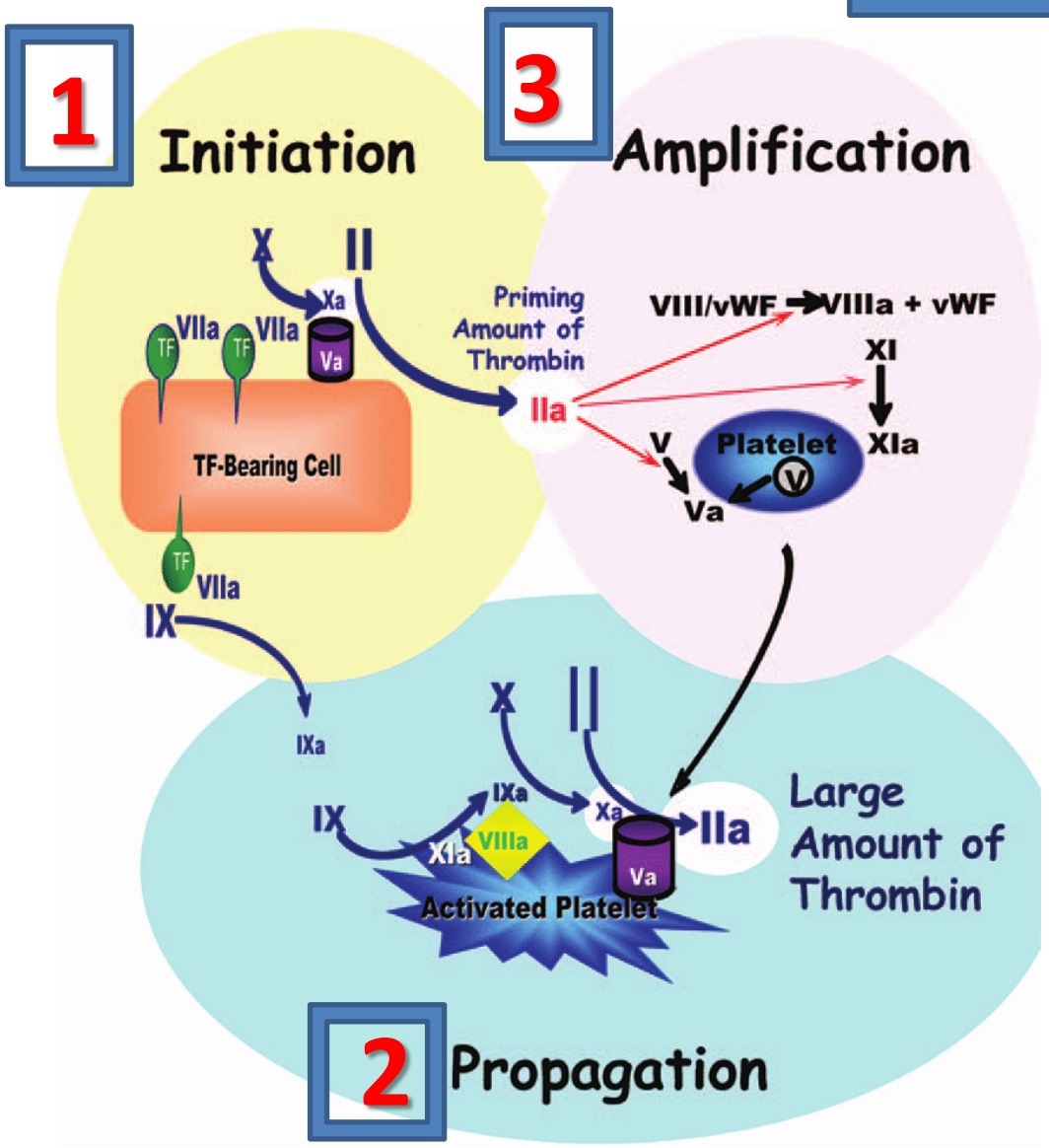
- Blood Clot:

  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++
X
Xa
X
Ca++, PL, VIII
Extrinsic system
tissue factor
VIIa
VII
Ca++
Final common pathway
Prothrombin II
Ca++, PL, V
thrombin IIa
XIII
XIIIa
Ca++
Fibrinogen I
Fibrin monomer
Fibrin

Cell-based model



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 (PF3)+ Ca ions activate factor X.
- Following this step the pathway is common for both intrinsic and extrinsic

Extrinsic pathway

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

Common pathway

- Activated factor X + factor V +PF3 + Ca activate prothrombin activator (proteolytic enzyme) which activates prothrombin.
- Activated prothrombin activates thrombin.
- Thrombin acts on fibrinogen and change it into fibrin monomers (soluble).
- Factor XIII + Calcium → strong fibrin multimers (strong clot)

Activation of Blood Coagulation

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

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

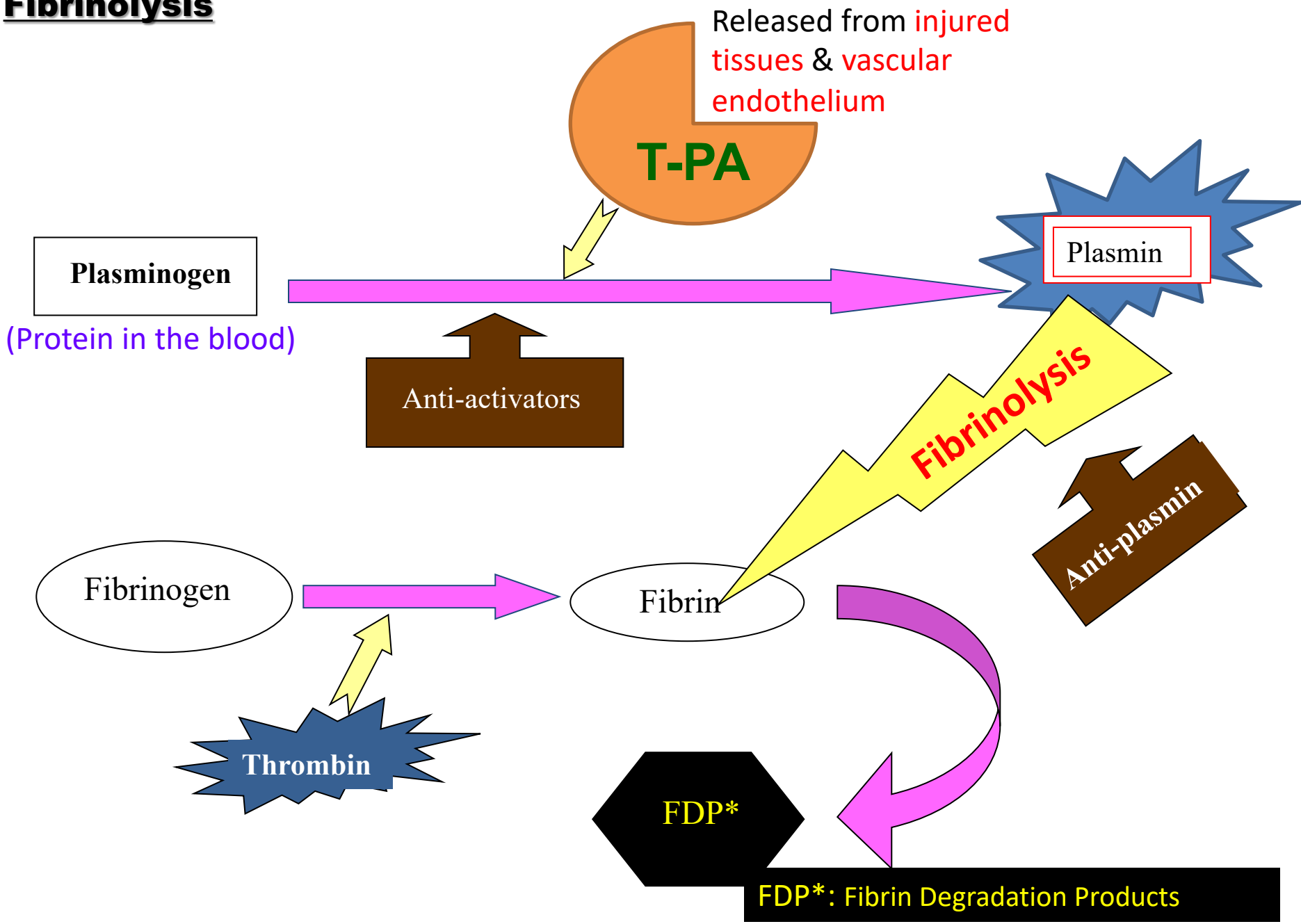
Fibrinolysis

- 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



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 *Cont.*

- **is controlled by:**
  - **Tissue Plasminogen Activator Inhibitor (TPAI)**
  - **Antiplasmin from the liver.**

- **Uses of TPA:**
  - **Tissue Plasminogen Activator is used to activate plasminogen to dissolve coronary/cerebral clots.**

Prevention of blood clotting in the normal vascular system & Anticoagulants

- Endothelial surface factors.
  - Smoothness of the ECS.
  - Glycocalyx layer.
  - Thrombomodulin protein.

- Fibrin fibers, adsorbs ~90% of thrombin to removes it from circulating blood.

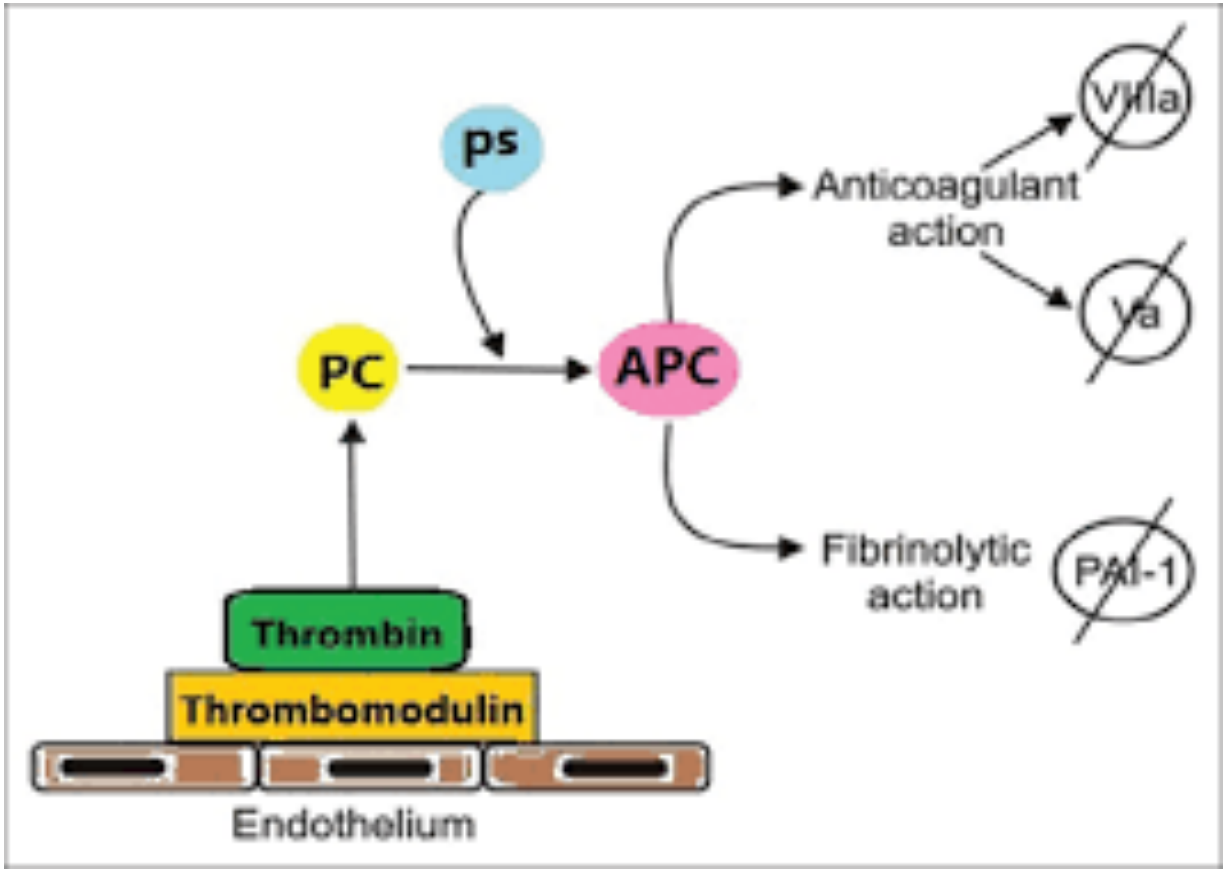
- Heparin, combines with Antithrombin III & quickly removes thrombin from blood (endothelial cells Liver, lungs, mast cells, basophils)

- Antithrombin III, removes the remaining thrombin from blood.

- Natural anticoagulant Proteins:
  - Protein C
  - Protein S

- **Actions of Protein C:**
  - Activate protein c (APC) degrades factors Va & VIIIa.
  - Activated protein C also indirectly promotes fibrinolysis.

- **Protein S is a cofactor for protein C.**



Conditions that cause excessive bleeding

- Vitamin K Deficiency:
- Prothrombin, Factor VII, Factor IX, Factor X require vitamin K for their synthesis.
- Hepatitis, Cirrhosis and GIT 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.

Hypercoagulability

Increased risk of thromboembolism.

Causes:

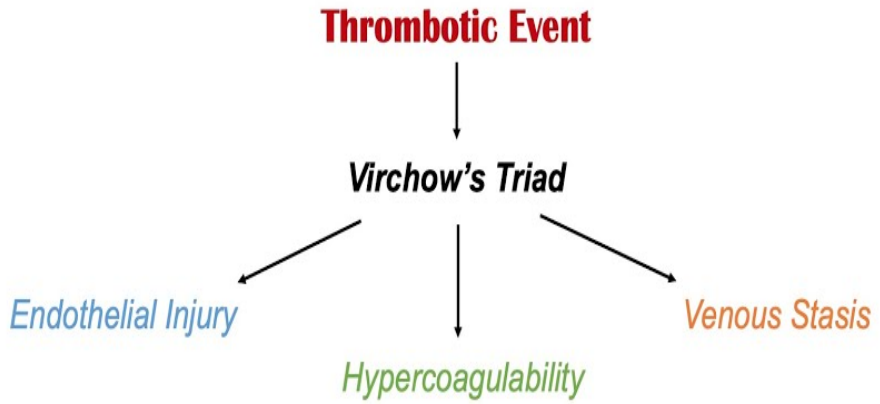
1- **Primary** (genetic):

(Thrombophilia)

2- **Secondary** (acquire

Approach to

Causes of Hypercoagulation



Congenital factors

- Resistance to activated protein C (Leiden Factor V)
- Mutation of the prothrombin gene (G20210A)
- Protein C deficit
- Protein S deficit
- Antithrombin III deficit
- Factor VIII increase (>1500 UI)
- Heparin Cofactor II deficiency
- Disfibrogenemia
- Plasminogen congenital deficiency
- Thrombomodulin mutation
- Sticky platelet syndrome
- Sickle cell anemia

Acquired factors

- Hepatic or endothelial pathology
- Vitamin C deficit
- Oral contraceptives
- Alcohol
- Tobacco
- Special situations:
  - Menopause
  - Pregnancy
  - Immobilization
  - Surgery
  - Traumatisms
- Diseases:
  - Cancer, myeloproliferative diseases
  - PTT
  - Disseminated intravascular coagulation
  - Sepsis
  - Hyperhomocysteinemia
  - Anti phospholipid antibody syndrome

Hypercoagulability