10
Coagulation Mechanisms

MED
433 Teams

GIT

OBJECTIVES

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

Recognize the different clotting factors

Understand the role of calcium ions during clotting cascades.

Describe the cascades of intrinsic and extrinsic pathways for clotting.

Recognize process of fibrinolysis and function of plasmin

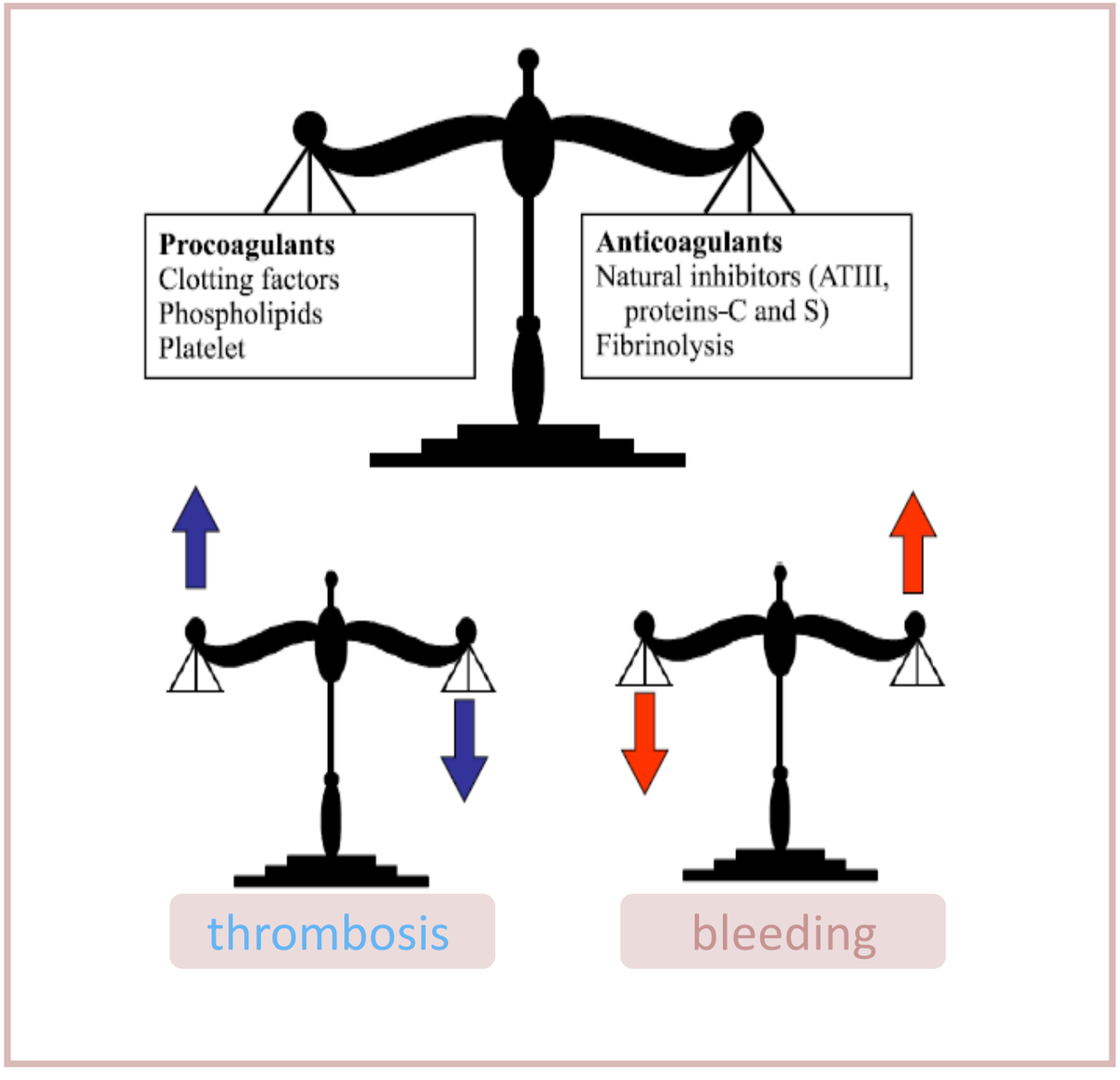
Recognize some conditions causing excessive bleeding

Understand some important anticoagulants and their mechanism of action

MECHANISM OF BLOOD COAGULATION

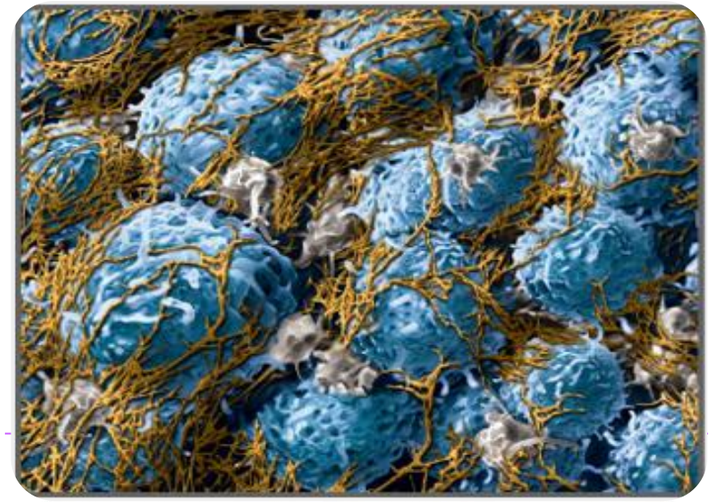
A crucial physiological balance exists between factors promoting coagulation (procoagulants) and factors inhibiting coagulation (anticoagulants).

Coagulation of blood depends on the balance between these two factors.
Disturbances in this balance could lead to thrombosis or bleeding



HEMOSTASIS:

prevention or stoppage of blood loss.

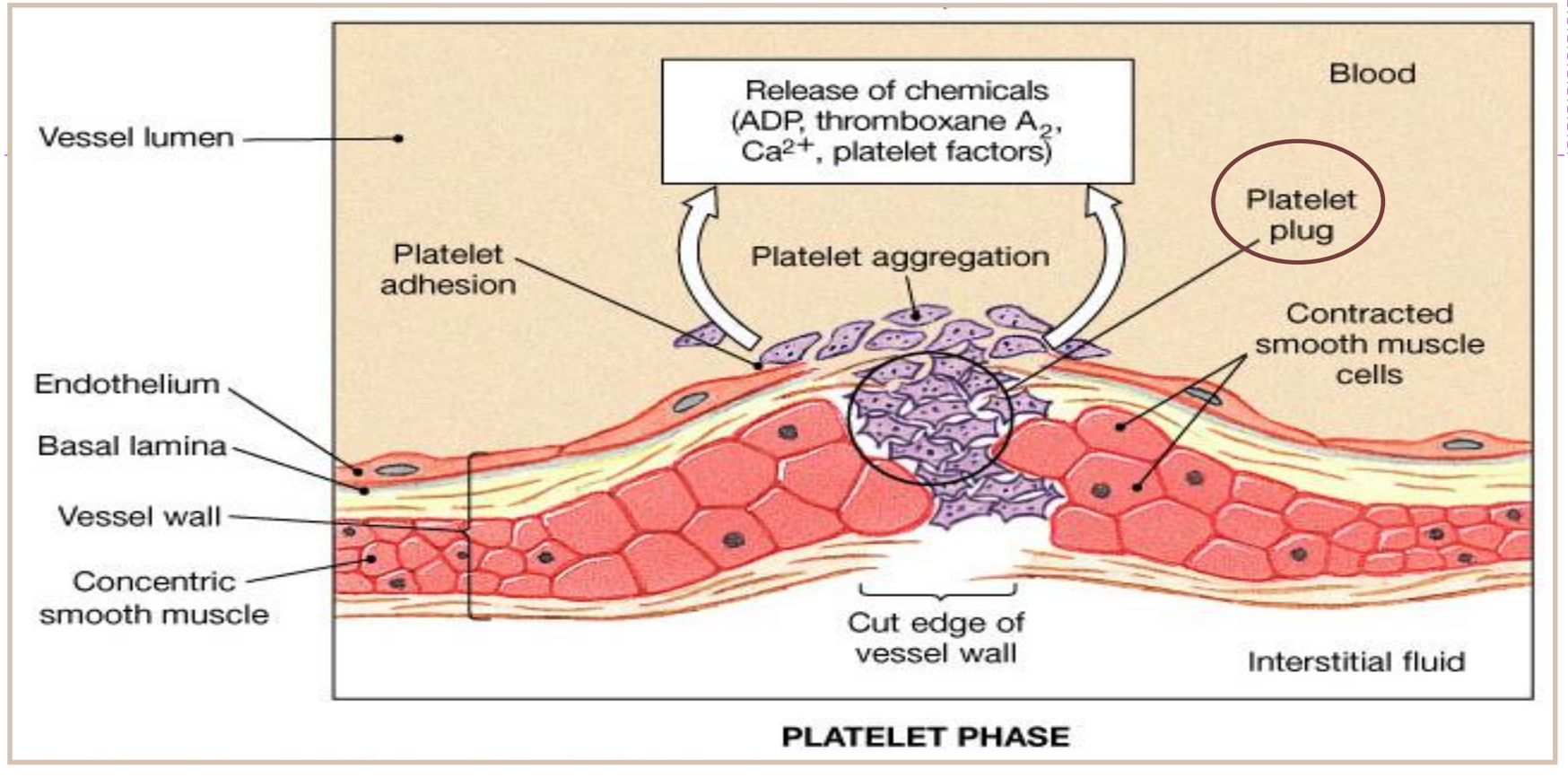


HEMOSTATIC MECHANISMS:

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	1	Fibrinogen
II	2	Prothrombin
III	3	Thromboplastin (tissue factor)
IV	4	Calcium
V	5	Labile factor
VII	7	Stable factor
VIII	8	Antihemophilic factor
IX	9	Antihemophilic factor B
X	10	Stuart-Prower factor
XI	11	Plasma thromboplastin antecedent (PTA)
XII	12	Hageman factor
XIII	13	Fibrin stablizing factors

Prothrombin (factor II):	**Thrombin**	**Fibrin-stabilizing factor (XIII):**	**Fibrinogen (factor I):**
- is a plasma protein, α2-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 **NOTE** 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**	**i**s 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	- 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	**-** is a high-molecular-weight plasma protein - it is continually formed by the liver - little or no fibrinogen leak from blood vessels

Intrinsic system

Kallik. ← Pre-K

HMWK

XII → XIIa Hageman factor A

Hageman factor 12

HMWK

11 (PTA) XI → XIa (PTA) A

Antihemophilic factor B IX → IXa

Ca^{++}

Stuart-Prower factor X → Xa ← X Stuart-Prower factor

Ca^{++}, PL, VIII

Extrinsic system

tissue factor

7 Stable factor A VIIa ← VII 7 Stable factor

Ca^{++}

Final common pathway

Prothrombin II → thrombin IIa

Ca^{++}, PL, V

Fibrin stablizing factors

XIII

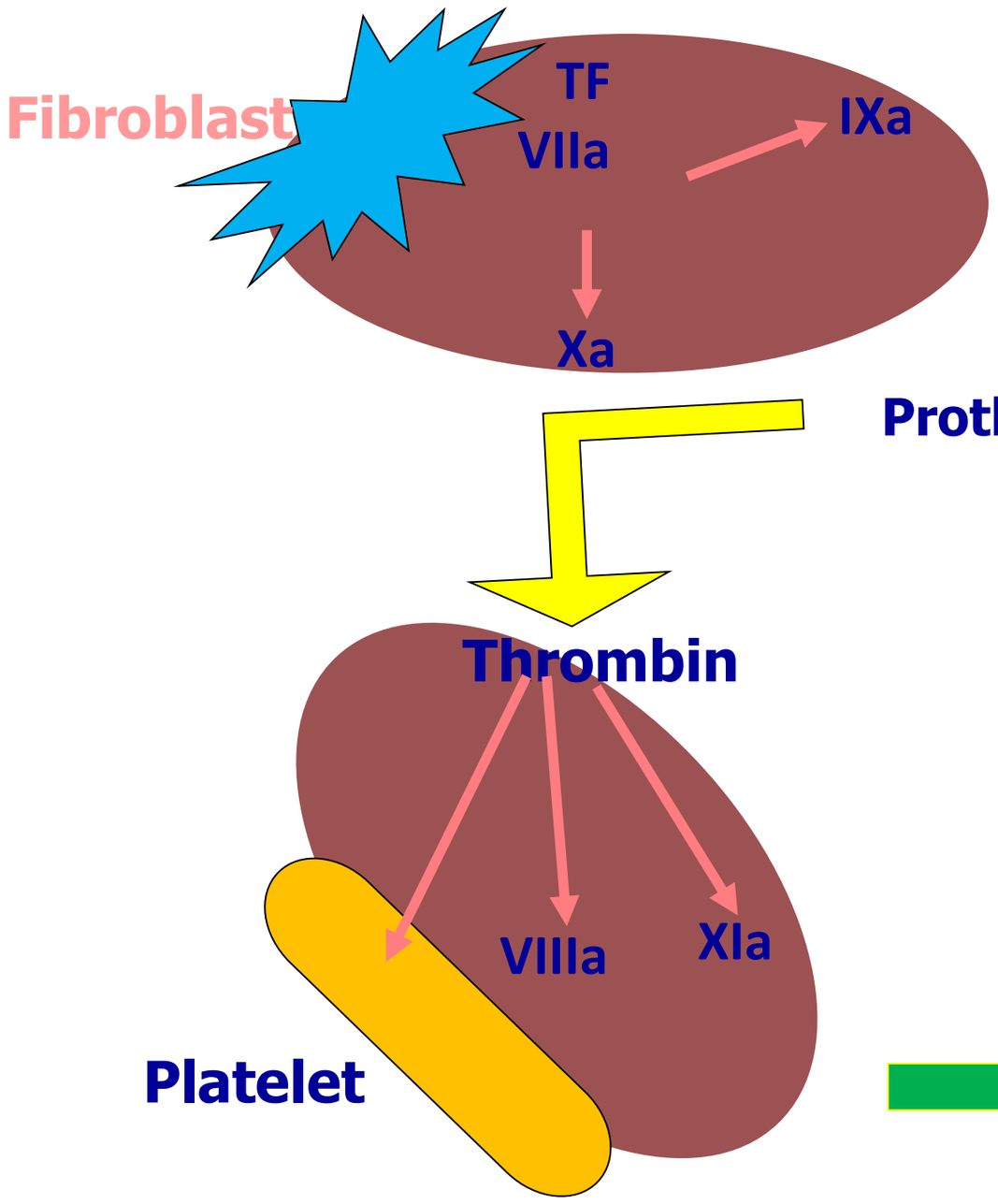
Fibrinogen I → Fibrin monomer → Fibrin

XIIIa

Ca^{++}

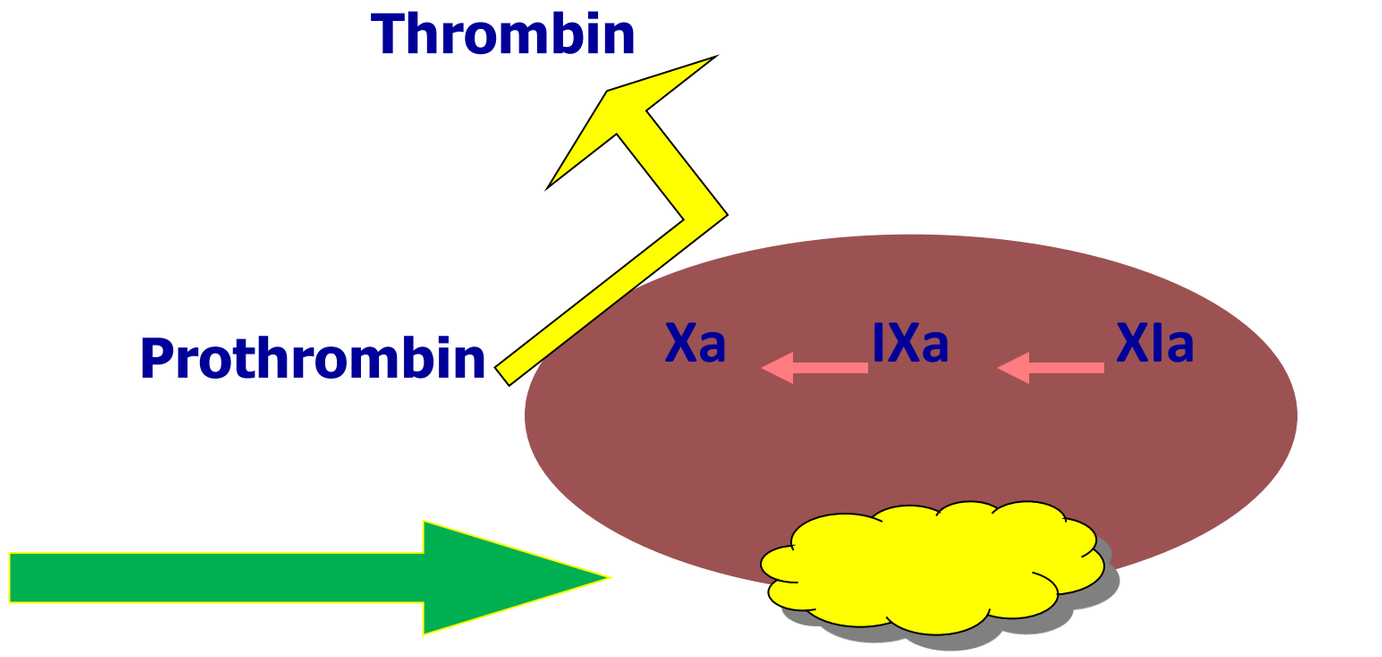
Cell based model

Initiation



Amplification

Propagation



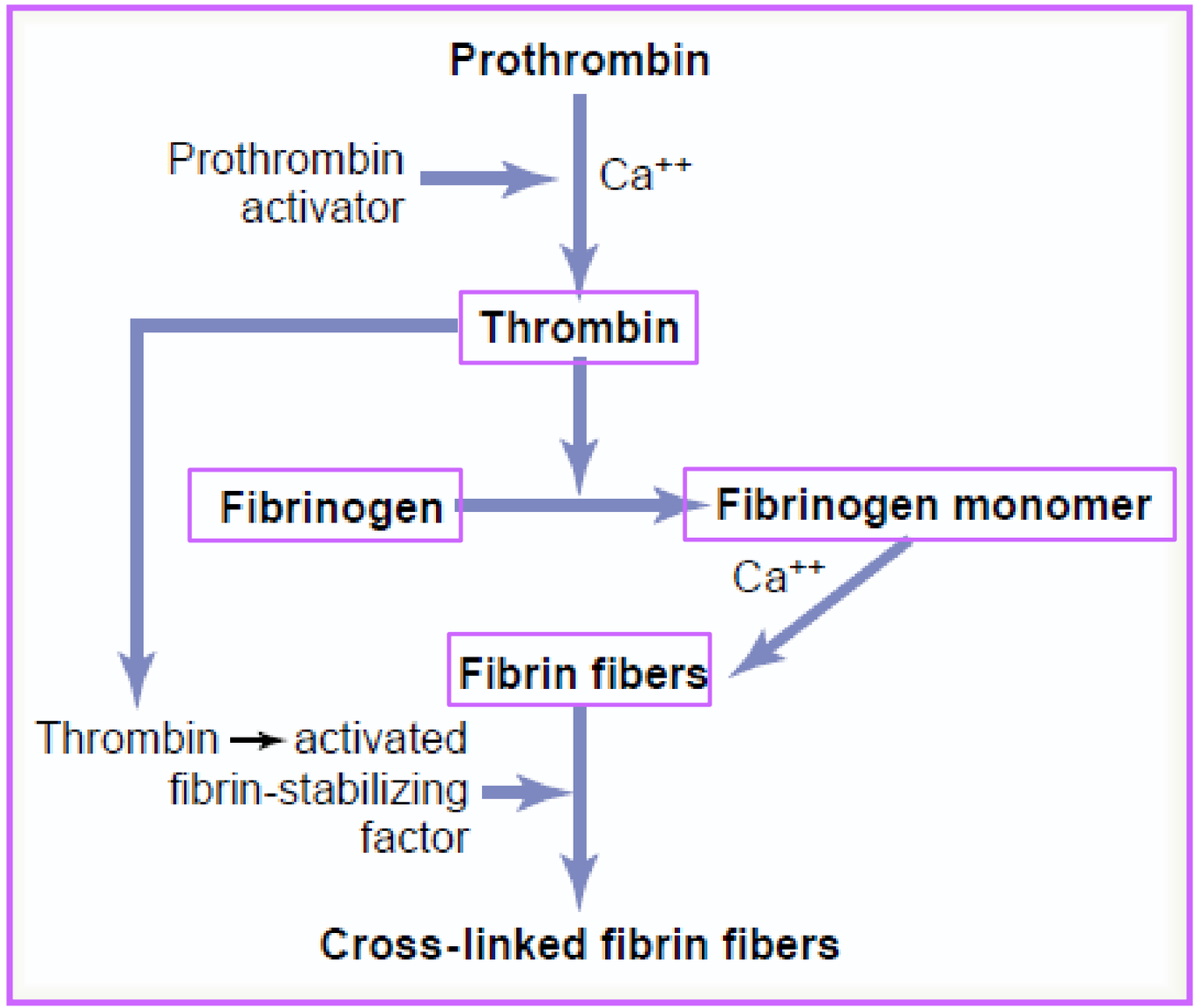
Blood Clot: •

- is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, plasma

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:



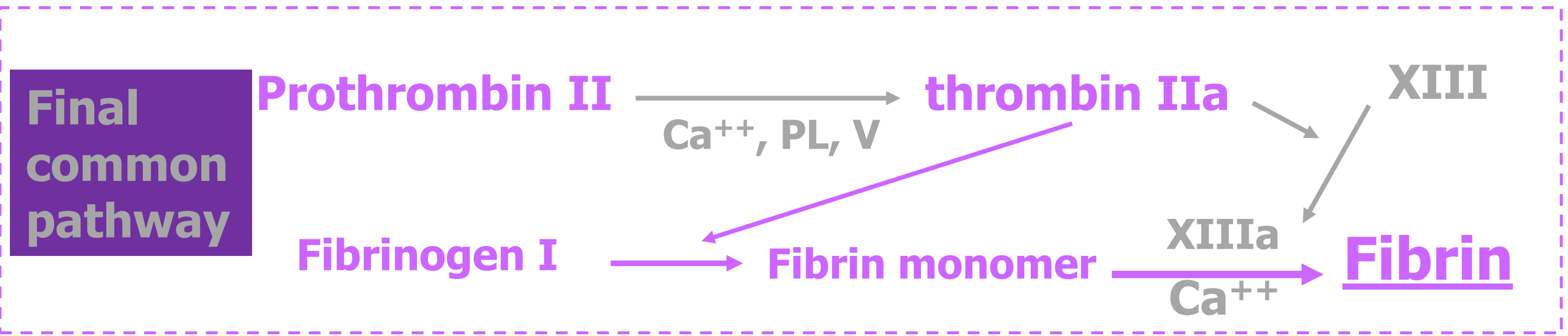
BLOOD COAGULATION (CLOT FORMATION):

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:

all clotting factors present in the blood

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 tissue factor (thromboplastin)

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)

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

It 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)

***Plasmin* digests fibrin fibers and some other protein such as fibrinogen, factor V, Factor VIII, Prothrombin, and factor XII. There for whenever a *Plasmin* is formed, it can cause lysis of a clot by destroying many of the clotting factors. (Unwanted effect of *plasmin* is the digestion of clotting factors) , sometimes even cause hypocoagulability of the blood .**

ACTIVATION OF PLASMINOGEN

When a clot is formed, a large amount of *Plasminogen* is trapped in the clot along with other plasma proteins. This will not become *Plasmin* or cause lysis of the clot until it activated. The injured tissues and vascular endothelium very slowly release a powerful activator called *tissue plasminogen activator (t-PA)* that a few days later, after the clot has stopped the bleeding, eventually converts *Plasminogen* to *Plasmin*, which in turn removes the remaining unnecessary blood clot.

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

PREVENTION OF BLOOD CLOTTING IN THE NORMAL VASCULAR SYSTEM AND ANTICOAGULANTS

Is done by :

1- Endothelial surface factors :

Smoothness of the Endothelial cell surface (ECS) which prevents contact activation of the intrinsic clotting system .

Glycocalyx layer: which repels clotting factors and platelets, thereby prevent activation of تصد أو تمنع التقاءهم clotting.

it binds with : Thrombomodulin protein thrombin and slow the clotting process and also it activates Protein C which act as an anticoagulant by inactivating activated factors V and VIII.

2- Fibrin fibers: adsorbs ~ 90% of thrombin to removes it from circulating blood (helps in preventing the spread of thrombin into the remaining blood, and therefor prevents excissive spread of the clot

3- The thrombin that doesn't adsorb to the fibrin fibers soon combines with antithrombin III, which further blocks the effect of the Thrombin on the fibrinogen and then also inactivate the thrombin itself.

4- Heparin: by itself, has little or no anticoagulant properties, but when it combines with antithrombin III, the effectiveness of antithrombin III increase.

Heparin is produced in basophilic mast cells located in the pericapillary connective tissue throughout the body

Mast cells are abundant in tissue surrounding the capillaries of the Lungs and liver. (it is needed here more than the other organs because the capillaries of lungs and liver receive many embolic clots formed in slowly flowing venous blood; sufficient formation of heparin prevents further growth of the clots).

Plasmin is controlled by

Tissue Plasminogen Activator Inhibitor (TPAI)

Antiplasmin from the liver

* Tissue Plasminogen Activator (TPA) used to activate plasminogen to dissolve coronary clots.

Conditions that cause excessive bleeding

Vitamin K deficiency

Vitamin K is essential for the liver to make Prothrombin, Factor VII, Factor IX, Factor X . In the absence of Vitamin K we will have insufficiency of these factors which will lead to bleeding.

Absence of Vit K could happen due to 3 reasons :

1. In normal person this can happen due to absence of Vit K from the diet.
2. In GIT disease as a result of poor absorption of fats from GIT (the reason of that is that Vit K is fat soluble and it need fats to be absorbed into the blood.
3. Lack of bile prevents adequate fat digestion and absorption as will. Thus, liver disease often causes decreased production of Prothrombin and some other clotting factors.

Hemophilia

Is a bleeding disease occurs almost exclusively in males (X chromosome linked disease) . In women if one of her X chromosomes is affected she will be a carrier and transmit the disease to half of her sons and transmit the carrier state to half of her daughters.

Hemophilia has two types :
1. hemophilia A or classic hemophilia : 85% due to Factor VIII deficiency.
2. hemophilia B : and 15% due to Factor IX deficiency .

Bleeding usually doesn't occur except after trauma, but the degree of bleeding is huge.

When a person with classic hemophilia experiences a sever prolonged bleeding, almost the only therapy that is truly effective is injection of purified factor VIII.

Thrombocytopenia

Very low number of platelets in blood (< 50,000/µl) .

The bleeding is usually from many small capillaries rather than from larger vessels as in hemophilia.

Most people with Thrombocytopenia have the disease known as idiopathic thrombocytopenia. In most of these people, it has been discovered that for unknown reasons, specific antibodies have formed and react against the platelets themselves to destroy them.

Treatment :
1. whole blood transfusion (effective for few days).
2. Spleenectomy (sometimes it's effective almost causing complete cure).

Some Important Anticoagulants

1\ Heparin: causes the blood clotting time to increase and this change in clotting time occurs instantaneously, thereby immediately preventing or slowing the development of the clots. Lasts for 1.5-4 Hours. The injected heparin is destroyed by an enzyme in the blood known as heparinase.

2\ Coumarins such as Warfarin: Warfarin inhibits the enzyme which activates Vitamin K (inhibits VKOR c1) thereby prevent activating of most of the clotting factors. It's effect is not immediate.

* Tissue Plasminogen Activator (TPA) used to activate plasminogen to dissolve coronary clots.

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GOOD LUCK