COAGULATION OF BLOOD

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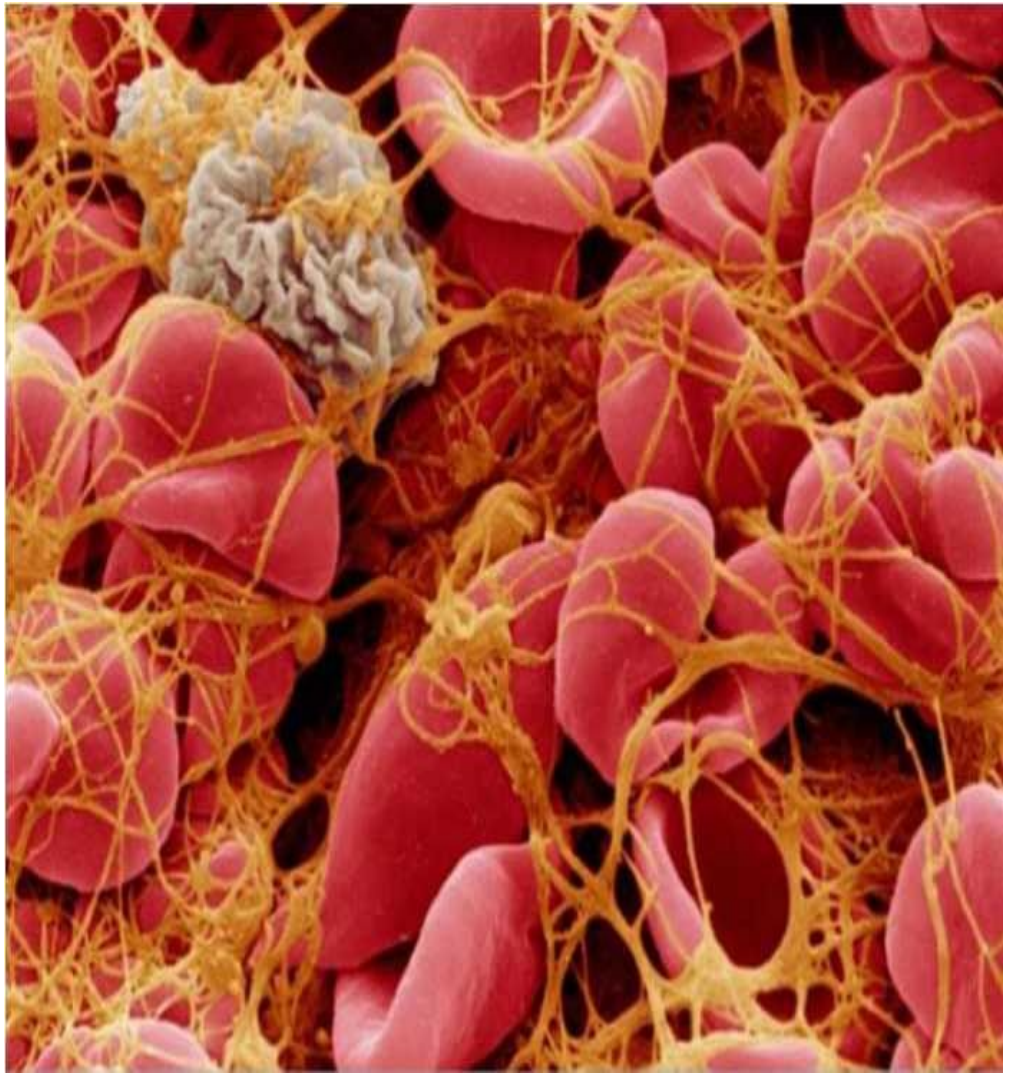
What is Coagulation?

- Coagulation or clotting is defined as the process in which blood loses its fluidity and becomes a jelly-like mass few minutes after it is shed out or collected in a container.



FACTORS INVOLVED IN BLOOD CLOTTING

- Coagulation of blood occurs through a series of reactions due to the activation of a group of substances.
- Substances necessary for clotting are called clotting factors.
- Thirteen clotting factors are identified:

Factor I Fibrinogen
Factor II Prothrombin
Factor III Thromboplastin (Tissue factor)
Factor IV Calcium
Factor V Labile factor (Proaccelerin or accelerator globulin)
Factor VI Presence has not been proved

Factor VII Stable factor
Factor VIII Antihemophilic factor (Antihemophilic globulin)
Factor IX Christmas factor
Factor X Stuart-Prower factor
Factor XI Plasma thromboplastin antecedent
Factor XII Hageman factor (Contact factor)
Factor XIII Fibrin-stabilizing factor (Fibrinase).

- Clotting factors were named after the scientists who discovered them or as per the activity, except factor IX.
- Factor IX or Christmas factor was named after the patient in whom it was discovered.

SEQUENCE OF CLOTTING MECHANISM

ENZYME CASCADE THEORY

- Enzyme cascade theory explains how various reactions, involved in the conversion of proenzymes to active enzymes take place in the form of a cascade.
- Most of the clotting factors are proteins in the form of enzymes.
- Normally, all the factors are present in the form of inactive **proenzyme.**
- By a series of proenzyme-enzyme conversion reactions They must be activated into enzymes to enforce clot formation.
- First one of the series is converted into an active enzyme that activates the second one, which activates the third one; this continues till the final active enzyme thrombin is formed.

STAGES OF BLOOD CLOTTING

- In general, blood clotting occurs in three stages:
  1. **Formation of prothrombin activator**
  2. **Conversion of prothrombin into thrombin**
  3. **Conversion of fibrinogen into fibrin.**

STAGE 1: FORMATION OF PROTHROMBIN ACTIVATOR

- Blood clotting commences with the formation of a substance called prothrombin activator, which converts prothrombin into thrombin.
- Its formation is initiated by substances produced either within the blood or outside the blood.

- Thus, formation of prothrombin activator occurs through two pathways:
  I. **Intrinsic pathway**
  II. **Extrinsic pathway**

I. INTRINSIC PATHWAY FOR THE FORMATION OF PROTHROMBIN ACTIVATOR

- In this pathway, the formation of prothrombin activator is initiated by platelets, which are within the blood itself

Sequence of Events in Intrinsic pathway

i. During the injury, the blood vessel is ruptured. Endothelium is damaged and collagen beneath the endothelium is exposed.
ii. When factor XII (Hageman factor) comes in contact with collagen, it is converted into activated factor XII in the presence of **kallikrein** and high molecular weight (HMW) **kinogen.**

iii. The activated factor XII converts factor XI into activated factor XI in the presence of HMW Kinogen.
iv. The activated factor XI activates factor IX in the presence of factor IV (calcium).
v. Activated factor IX activates factor X in the presence of factor VIII and calcium.
vi. When platelet comes in contact with collagen of damaged blood vessel, it gets activated and releases phospholipids.
vii. Now the activated factor X reacts with platelet phospholipid and factor V to form prothrombin activator. This needs the presence of calcium ions.
viii. Factor V is also activated by positive feedback effect of thrombin.

II. EXTRINSIC PATHWAY FOR THE FORMATION OF PROTHROMBIN ACTIVATOR

- In this pathway, the formation of prothrombin activator is initiated by the tissue thromboplastin, which is formed from the injured tissues.

Sequence of Events in Extrinsic Pathway

i. Tissues that are damaged during injury release tissue thromboplastin (factor III). Thromboplastin contains proteins, phospholipid and glycoprotein, which act as proteolytic enzymes.
ii. Glycoprotein and phospholipid components of thromboplastin convert factor X into activated factor X, in the presence of factor VII.
iii. Activated factor X reacts with factor V and phospholipid component of tissue thromboplastin to form prothrombin activator. This reaction requires the presence of calcium ions.

STAGE 2: CONVERSION OF PROTHROMBIN INTO THROMBIN

- Blood clotting is all about thrombin formation.
- Once thrombin is formed, it definitely leads to clot formation.

Sequence of Events in Stage 2

i. Prothrombin activator that is formed in intrinsic and extrinsic pathways converts prothrombin into thrombin in the presence of calcium (factor IV).
ii. Once formed thrombin initiates the formation of more thrombin molecules. The initially formed thrombin activates Factor V. Factor V in turn accelerates formation of both extrinsic and intrinsic prothrombin activator, which converts prothrombin into thrombin.

- This effect of thrombin is called **positive feedback** effect.

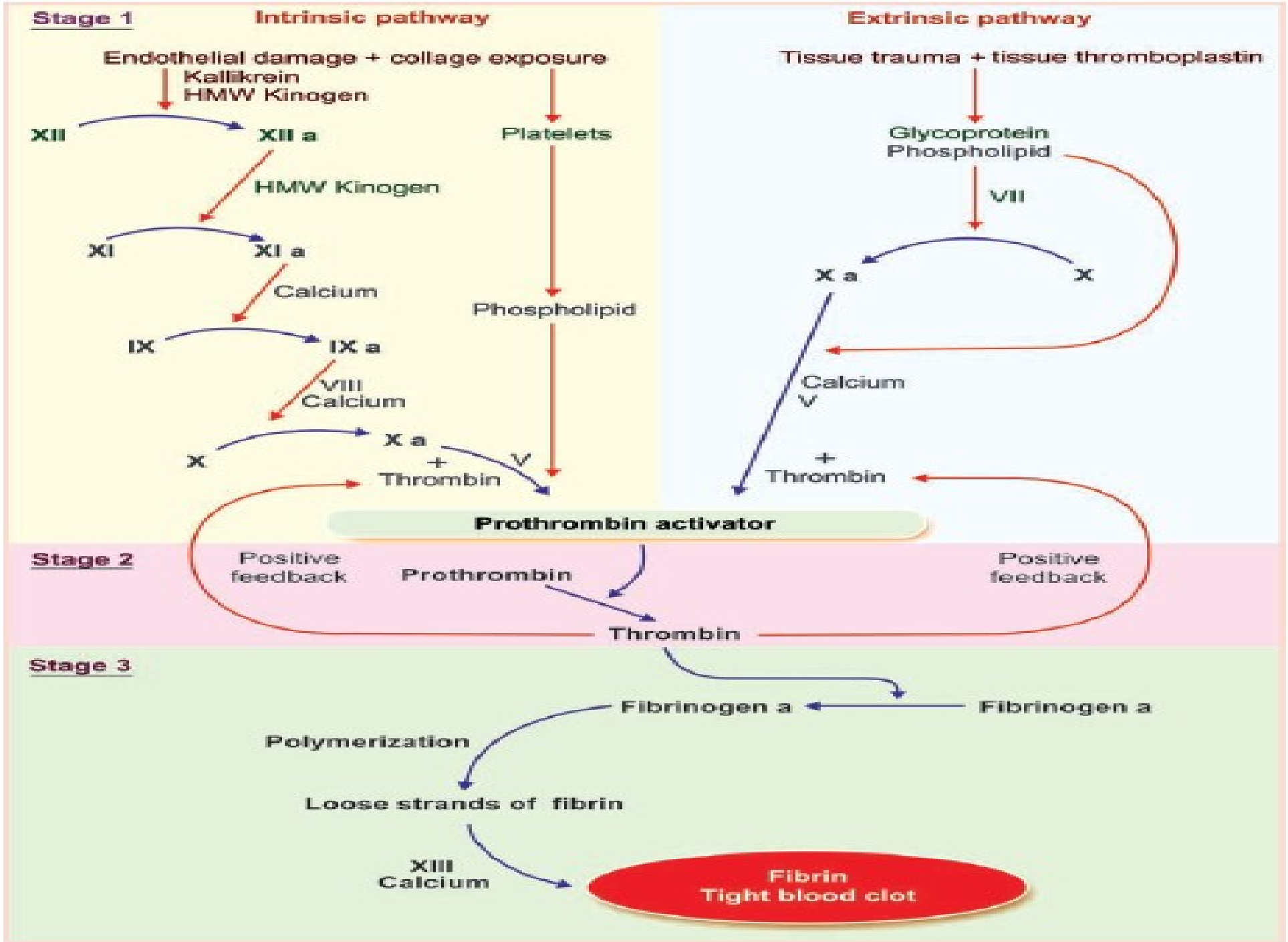
STAGE 3: CONVERSION OF FIBRINOGEN INTO FIBRIN

- The final stage of blood clotting involves the conversion of fibrinogen into fibrin by thrombin.

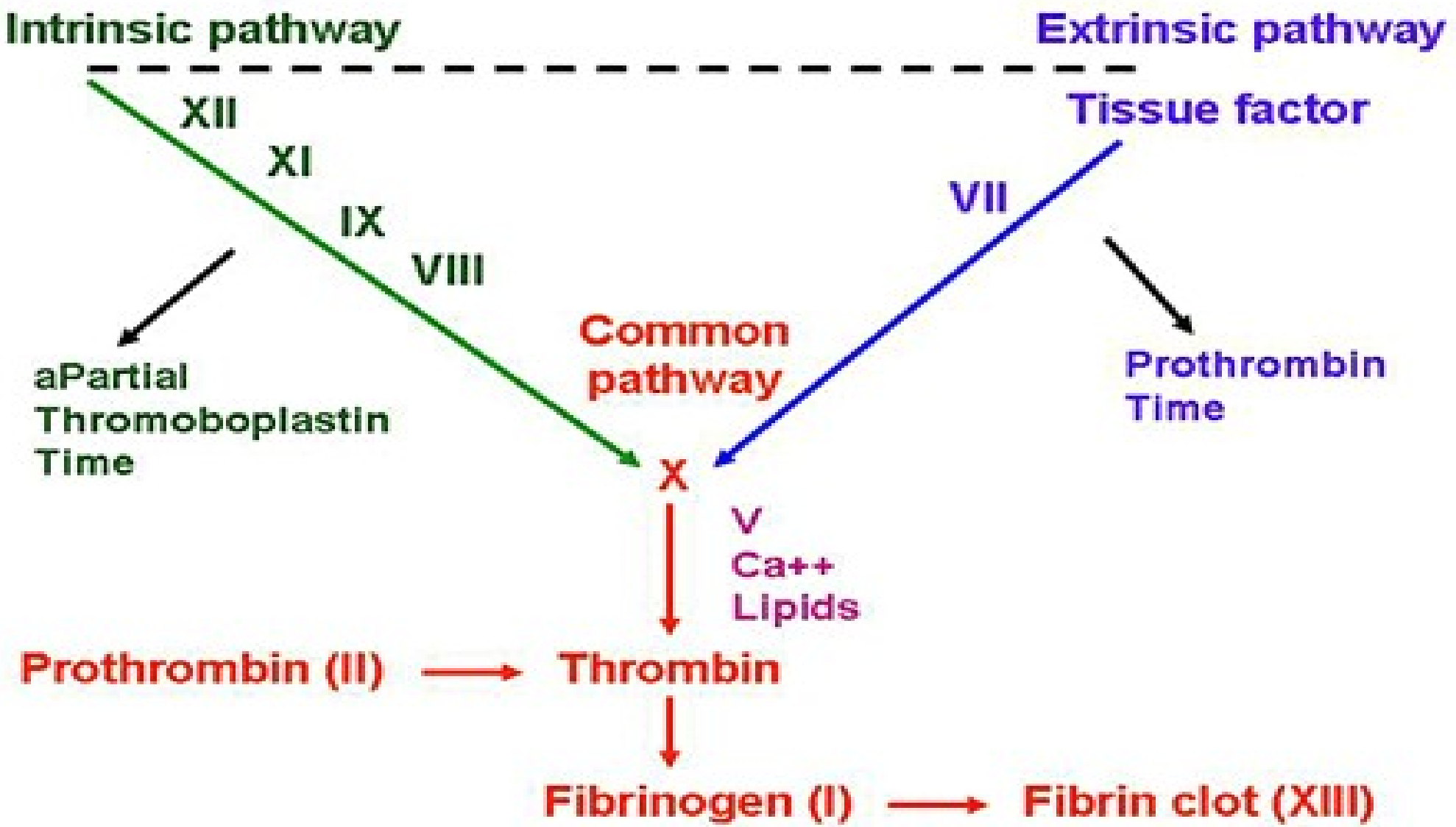
Sequence of Events in Stage 3

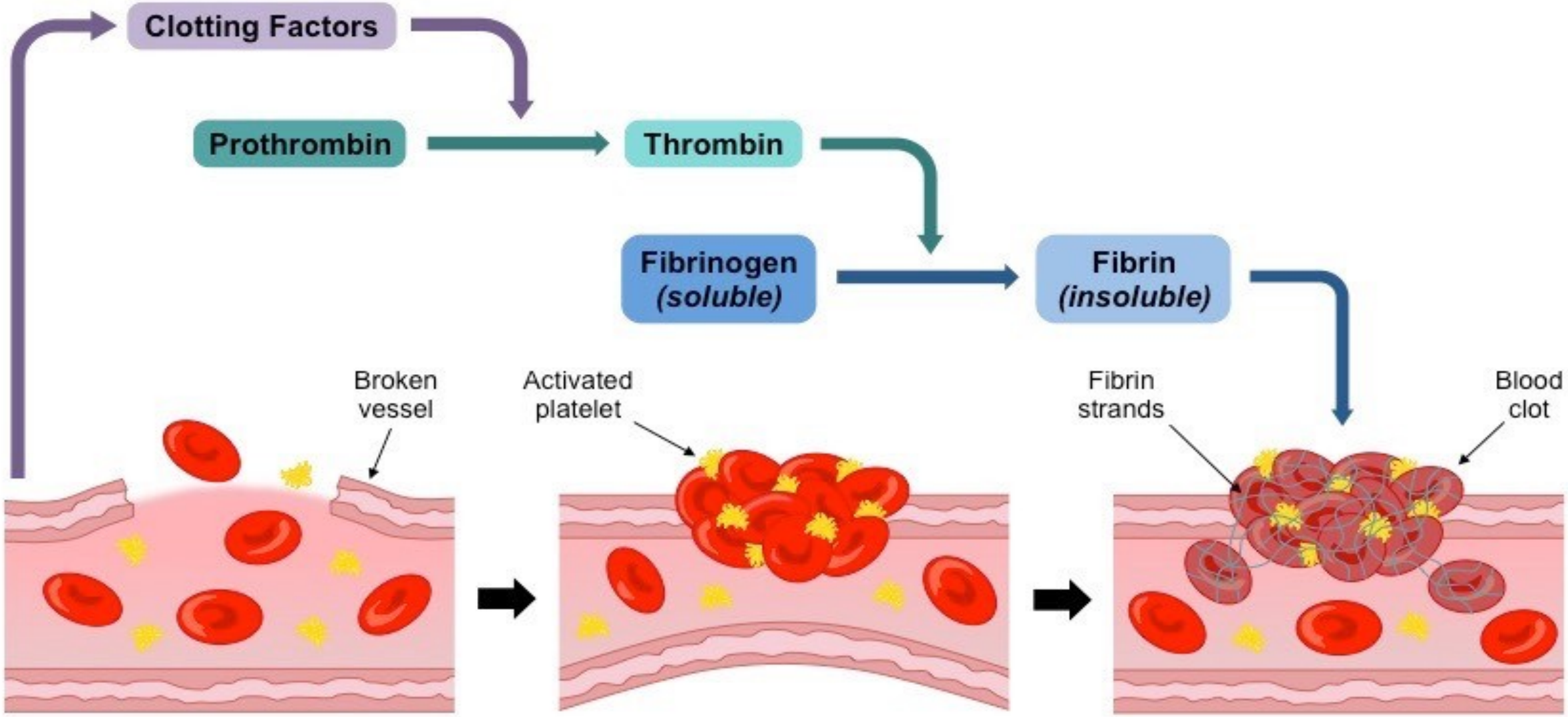
i. Thrombin converts inactive fibrinogen into activated fibrinogen due to loss of 2 pairs of polypeptides from each fibrinogen molecule. The activated fibrinogen is called **fibrin monomer.**
ii. Fibrin monomer polymerizes with other monomer molecules and form loosely arranged strands of fibrin.
iii. Later these loose strands are modified into dense and tight fibrin threads by fibrin-stabilizing factor (factor XIII) in the presence of calcium ions.

- All the tight fibrin threads are aggregated to form a meshwork of **stable clot.**


Stage 1
Intrinsic pathway
Endothelial damage + collage exposure
Kallikrein
HMW Kinogen
XII
XII a
HMW Kinogen
XI
XI a
Calcium
IX
IX a
VIII
Calcium
X
X a
+
Thrombin
V
Platelets
Phospholipid
Extrinsic pathway
Tissue trauma + tissue thromboplastin
Glycoprotein
Phospholipid
VII
X a
X
Calcium
V
+
Thrombin
Prothrombin activator
Stage 2
Positive
feedback
Prothrombin
Positive
feedback
Thrombin
Stage 3
Fibrinogen a
Fibrinogen a
Polymerization
Loose strands of fibrin
XIII
Calcium
Fibrin
Tight blood clot

Coagulation Cascade





Damaged Blood Vessel
Injury to vessel lining triggers the release of clotting factors

Formation of Platelet Plug
Vasoconstriction limits blood flow and platelets form a sticky plug

Development of Clot
Fibrin strands adhere to the plug to form an insoluble clot

BLOOD CLOT

- Blood clot is defined as the mass of coagulated blood which contains RBCs, WBCs and platelets entrapped in fibrin meshwork.
- The external blood clot is also called scab. It adheres to the opening of damaged blood vessel and prevents blood loss.

ANTICLOTTING MECHANISM IN THE BODY

- Under physiological conditions, intravascular clotting does not occur.
- It is because of the presence of some physicochemical factors in the body.

A. PHYSICAL FACTORS

- Continuous circulation of blood.
- Smooth endothelial lining of the blood vessels.

B. CHEMICAL FACTORS – NATURAL ANTICOAGULANTS

i. Presence of natural anticoagulant called heparin that is produced by the liver
ii. Production of thrombomodulin by endothelium of the blood vessels (except in brain capillaries). Thrombomodulin is a thrombin-binding protein. It binds with thrombin and forms a thrombomodulin thrombin complex. This complex activates protein C. Activated protein C along with its cofactor protein S inactivates Factor V and Factor VIII. Inactivation of these two clotting factors prevents clot formation
iii. All the clotting factors are in inactive state.

ANTICOAGULANTS

- Substances which prevent or postpone coagulation of blood are called anticoagulants.
- Anticoagulants are of three types:

1. Anticoagulants used to prevent blood clotting inside the body, i.e. in vivo.
2. Anticoagulants used to prevent clotting of blood that is collected from the body, i.e. in vitro.
3. Anticoagulants used to prevent blood clotting both in vivo and in vitro.

A. HEPARIN

- Heparin is a naturally produced anticoagulant in the body.
- It is produced by **mast cells.**
- Basophils also secrete heparin.

B. EDTA

- Ethylene diamine tetra acetic acid (EDTA) is a strong anticoagulant. It is available in two forms:
  i. Disodium salt (Na2 EDTA).
  ii. Tripotassium salt (K3 EDTA).

C. CITRATES

- Sodium, ammonium and potassium citrates are used as anticoagulants.

D. OXALATE COMPOUNDS

- Oxalate compounds prevent coagulation by forming calcium oxalate, which is precipitated later. Thus, these compounds reduce the blood calcium level.