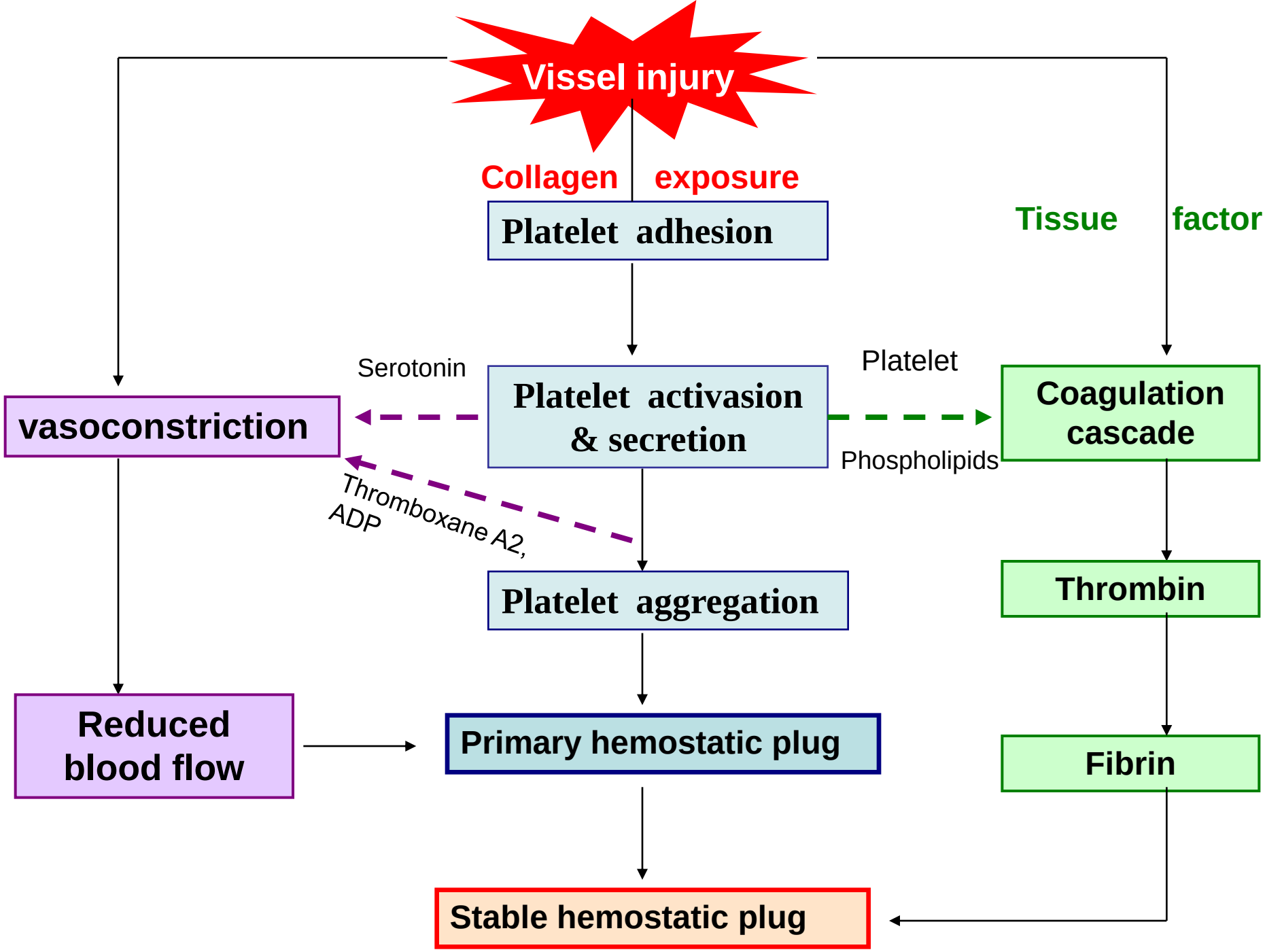
Hemostasis and coagulation

Hemostasis

- Is a complex process which causes the bleeding process to stop
- Primary Haemostais (Vessel wall, Platelets)
- Secondary Haemostsis (Coagulation Cascade)

3 Major systems involved

- **Vessel wall**
  - **Endothelium**
- **Platelets**
- **Coagulation cascade**
  - **Coagulation factors (proteins)**
    - **Names and numbers**
    - **Active and inactive forms (zymogens)**


Vissel injury
Collagen exposure
Tissue factor
Platelet adhesion
Serotonin
Platelet activasion & secretion
Platelet
Phospholipids
vasoconstriction
Coagulation cascade
Thromboxane A2, ADP
Platelet aggregation
Thrombin
Reduced blood flow
Primary hemostatic plug
Fibrin
Stable hemostatic plug

What happen when a BV injured?

1- **Vasoconstriction** of blood vessel.

2- **Platelet plug:** Platelets adhere to the site, activated, and change their shape and release granules.

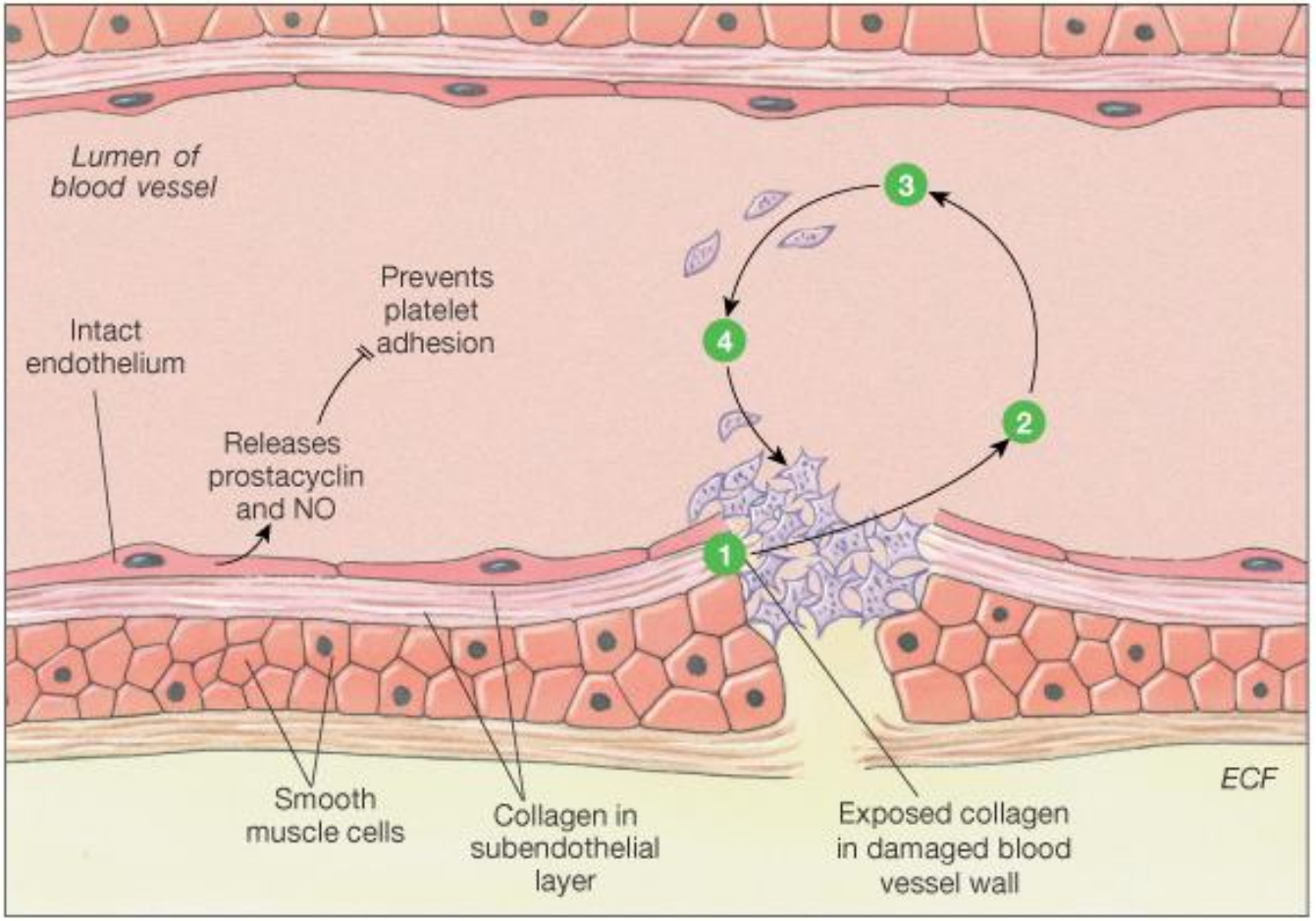
- Some granules promote vasoconstriction & other granules promote platelet aggregation and adhesion= unstable platelet plug.

3- **Coagulation** cascade is stimulated which result at the end in formation of stable fibrin clot.

Hemostasis flash video

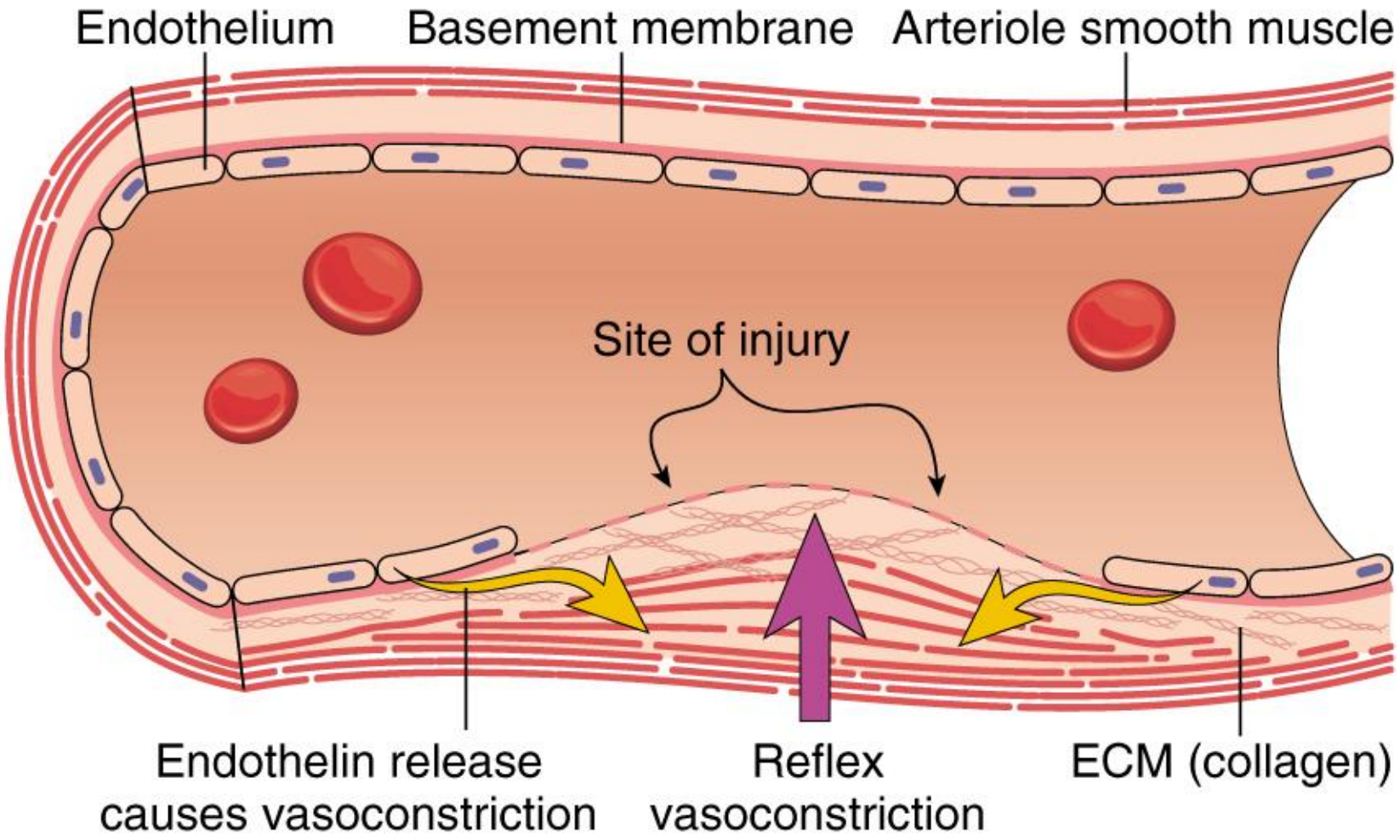
http://www.mhhe.com/biosci/esp/2002_general/Esp/folder_structure/tr/m1/s7/trm1s7_3.htm

Hemostasis: Vasoconstriction & Plug Formation



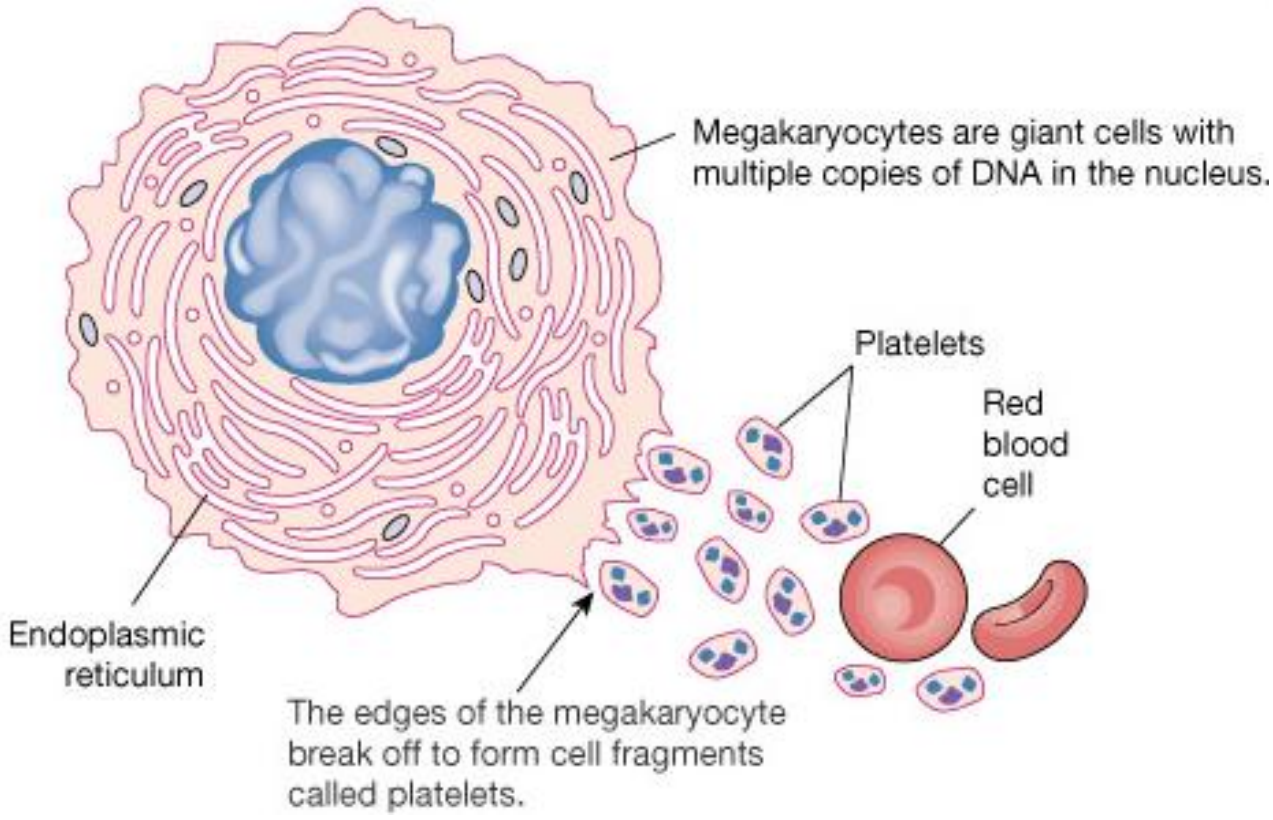
1. Exposed collagen binds and activates platelets.
2. Release of platelet factors
3. Attracts more platelets
4. Aggregate into platelet plug

A. VASOCONSTRICTION

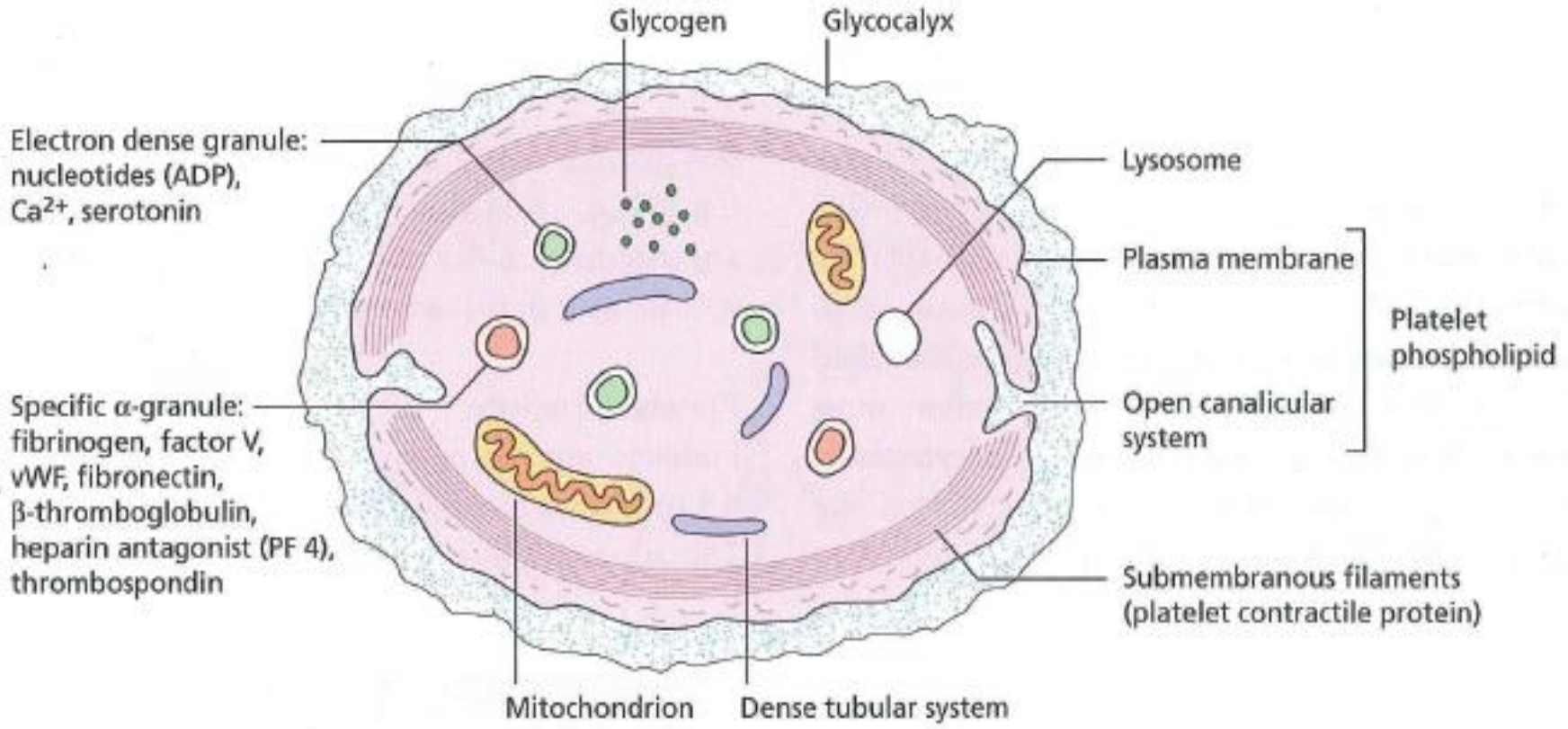


Platelets

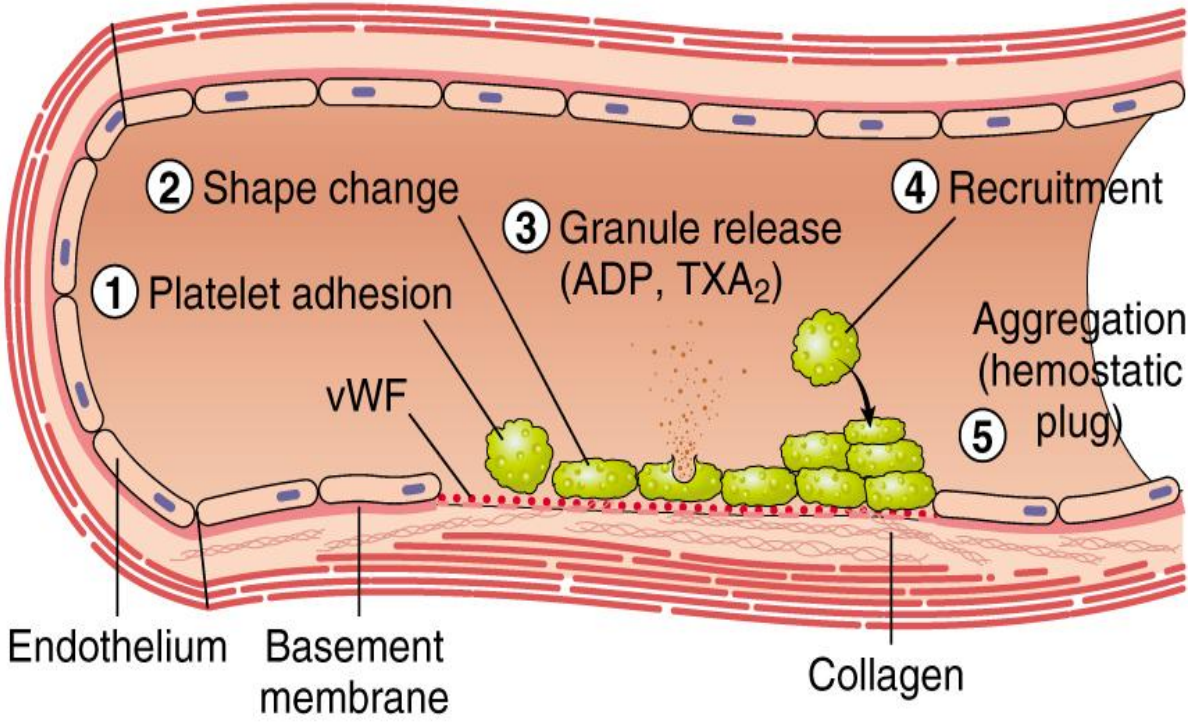
- Formed by fragmentation from megakaryoctyes

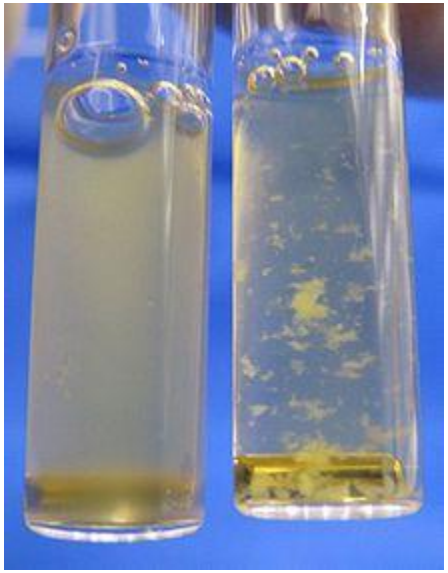


Platelet Structure

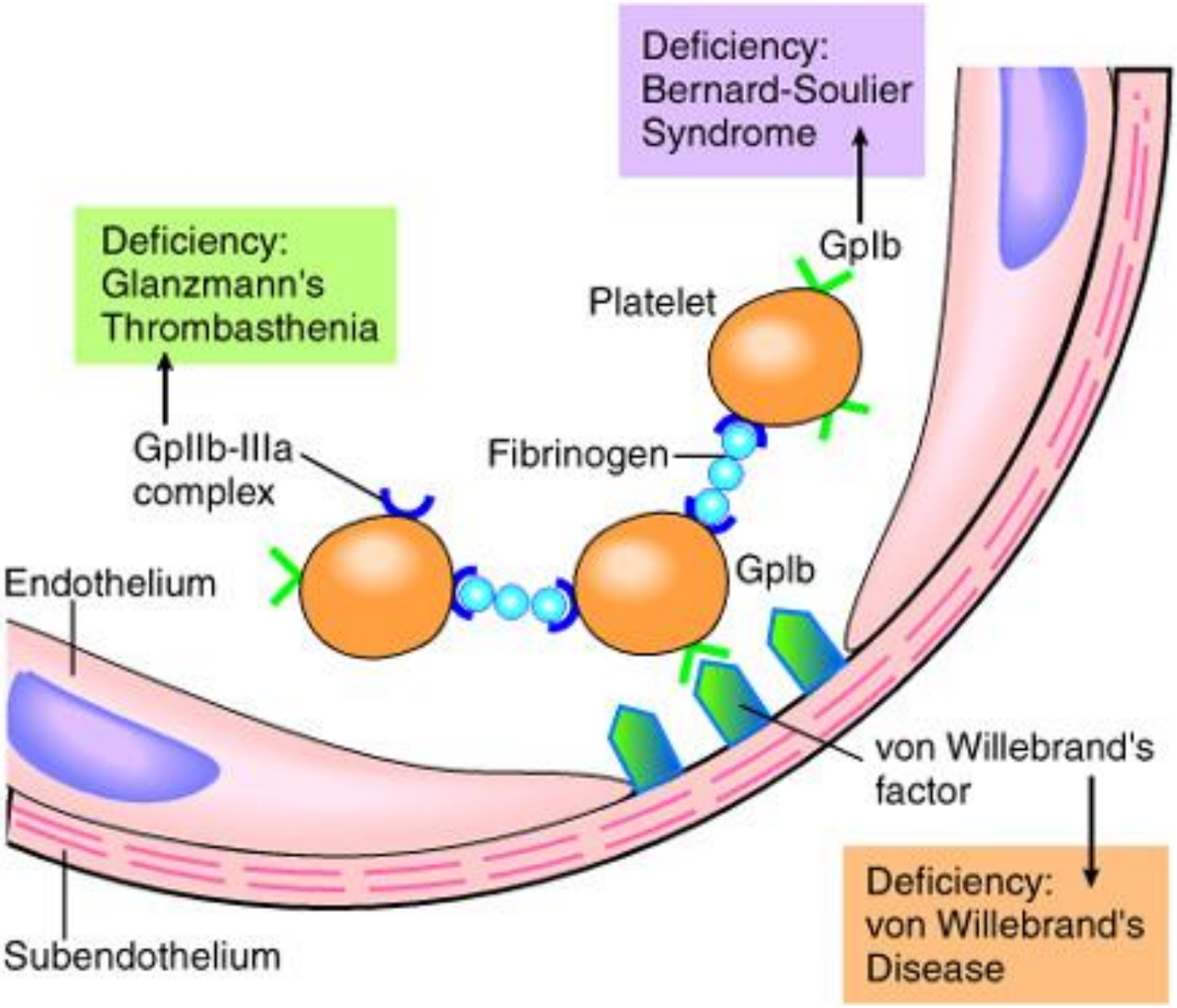


B. PRIMARY HEMOSTASIS

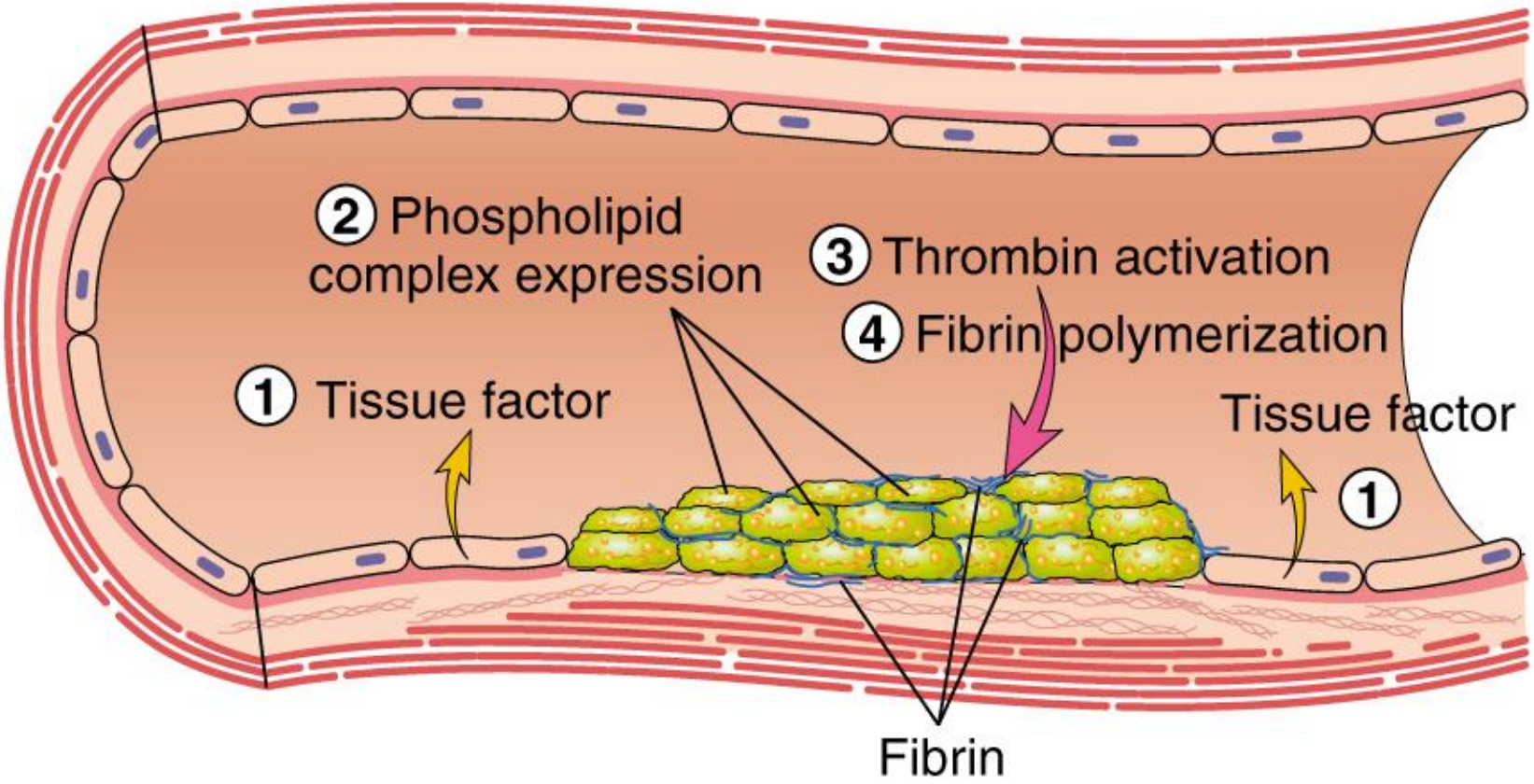




Addition of ADP to platelets = aggregation


Deficiency:
Bernard-Soulier
Syndrome
Deficiency:
Glanzmann's
Thrombasthenia
GpIb
Platelet
GpIIb-IIIa
complex
Fibrinogen
GpIb
Endothelium
von Willebrand's
factor
Deficiency:
von Willebrand's
Disease
Subendothelium

C. SECONDARY HEMOSTASIS



Endothelial cells

If blood vessel is intact:

1-They inhibit blood coagulation by secreting heparin like substances and thrombomodulin.

2- They inhibit platelet aggregation by secreting NO & prostacyclin.

If blood vessel is injured:

- They secrete substances that aid coagulation (Thromboplastin & VWF).

Coagulation Cascade

- Blood coagulation involves a number of substances which sequentially activate by proteolysis a cascade of circulating precursor proteins
- This results in the generation of thrombin
- Thrombin in turn converts soluble fibrinogen into fibrin
- Fibrin enmeshes the platelet aggregate and converts the unstable aggregate into stable haemostatic plug

Coagulation Cascade

- **All are serine proteases (except XIII)**
  - Produced by liver (most)
  - Require Vit K (several)
- **3 protein cofactors (not enzymes)**
- **Requires Ca^{2+}**
- **Localized to site of injury**
- **Reversible (via production of plasmin)**

Coagulation Cascade

- The generation of thrombin in vivo is a complex mechanism
- The generation of thrombin is dependent on three enzyme complexes (each contain: protease and cofactor)

1)The extrinisc Xase (TF, VIIa)

2)The intrinsic Xase (IX, VIIIa)

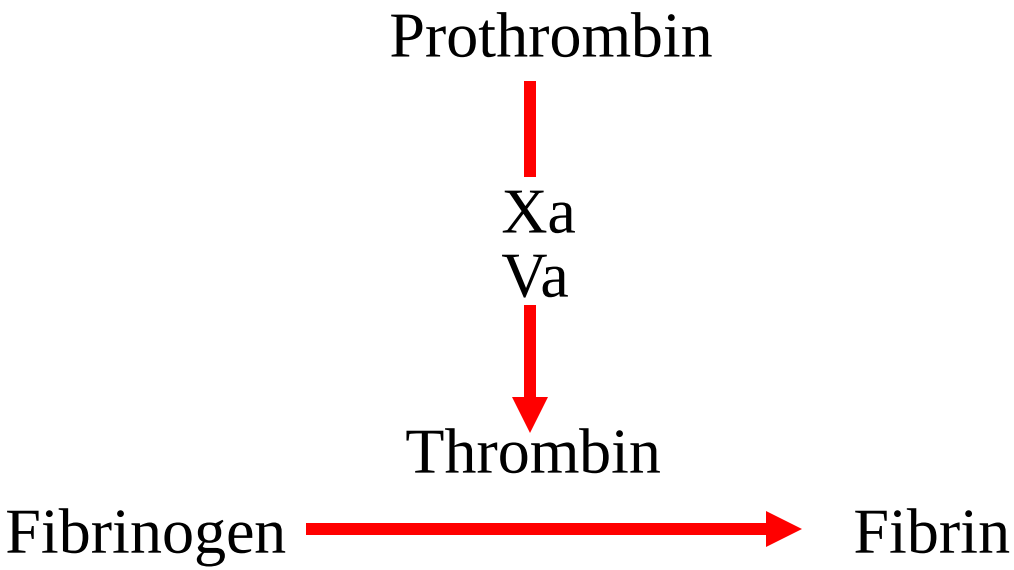
3)The above two enzymes generates the protrhombinase complex (Xa, Va)

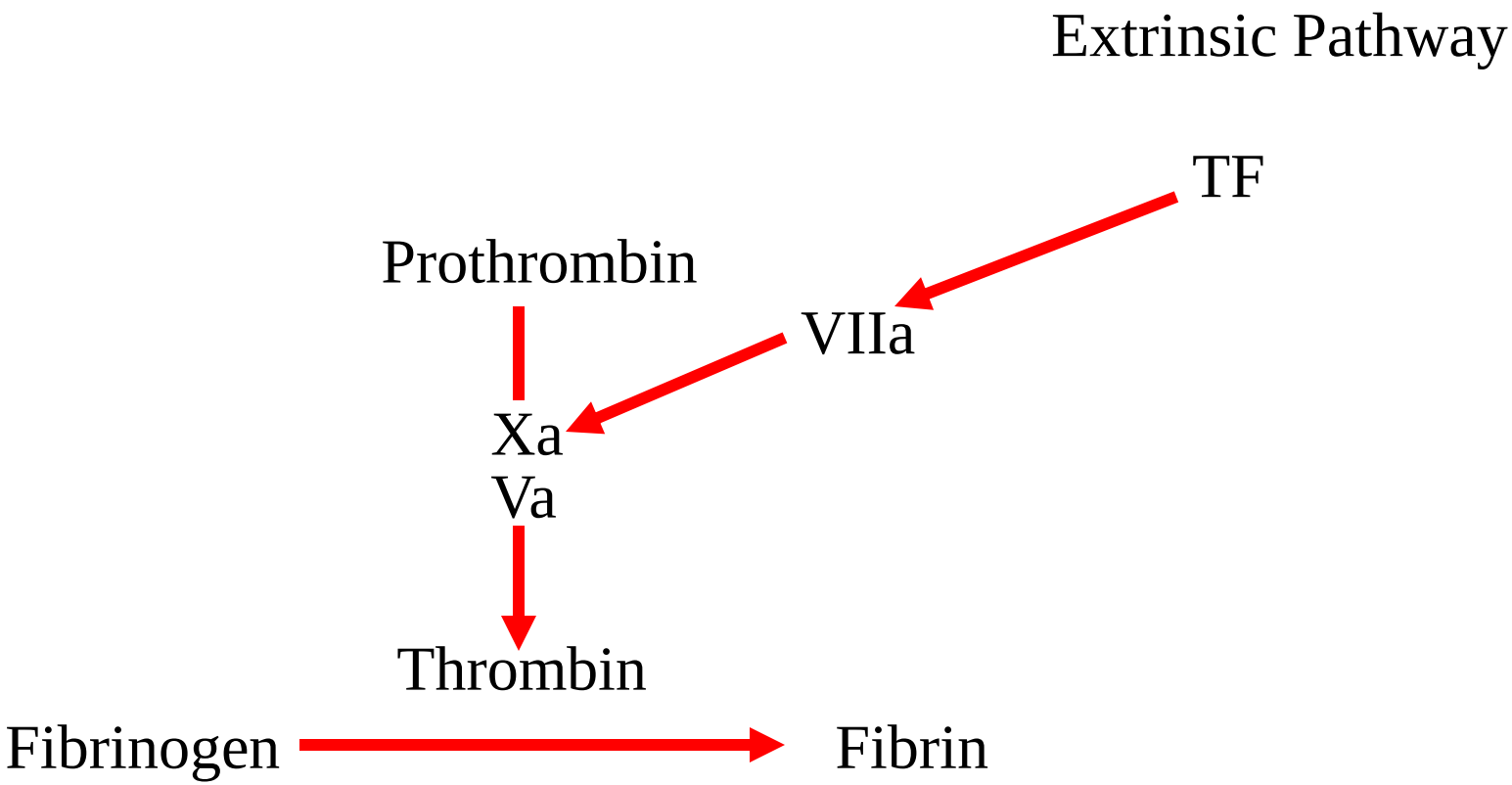
Coagulation process

- Damaged tissue releases factor III (TF), which with the aid of Ca^{++} will activate factor VII, thus initiating the extrinsic mechanism.
- Factor XII from active platelets will activate factor XI, thus initiating the intrinsic mechanism.
- Both active factor VII and active factor XI will promote cascade reactions, eventually activating factor X.
- Active factor X, along with factor III, factor V, Ca^{++}, and platelet thromboplastic factor (PF_3), will activate prothrombin activator.
- Prothrombin activator converts prothrombin to thrombin.
- Thrombin converts fibrinogen to fibrin.
- Fibrin initially forms a loose mesh, but then factor XIII causes the formation of covalent cross links, which convert fibrin to a dense aggregation of fibers.
- Platelets and red blood cells become caught in this mesh of fiber, thus the formation of a blood clot.

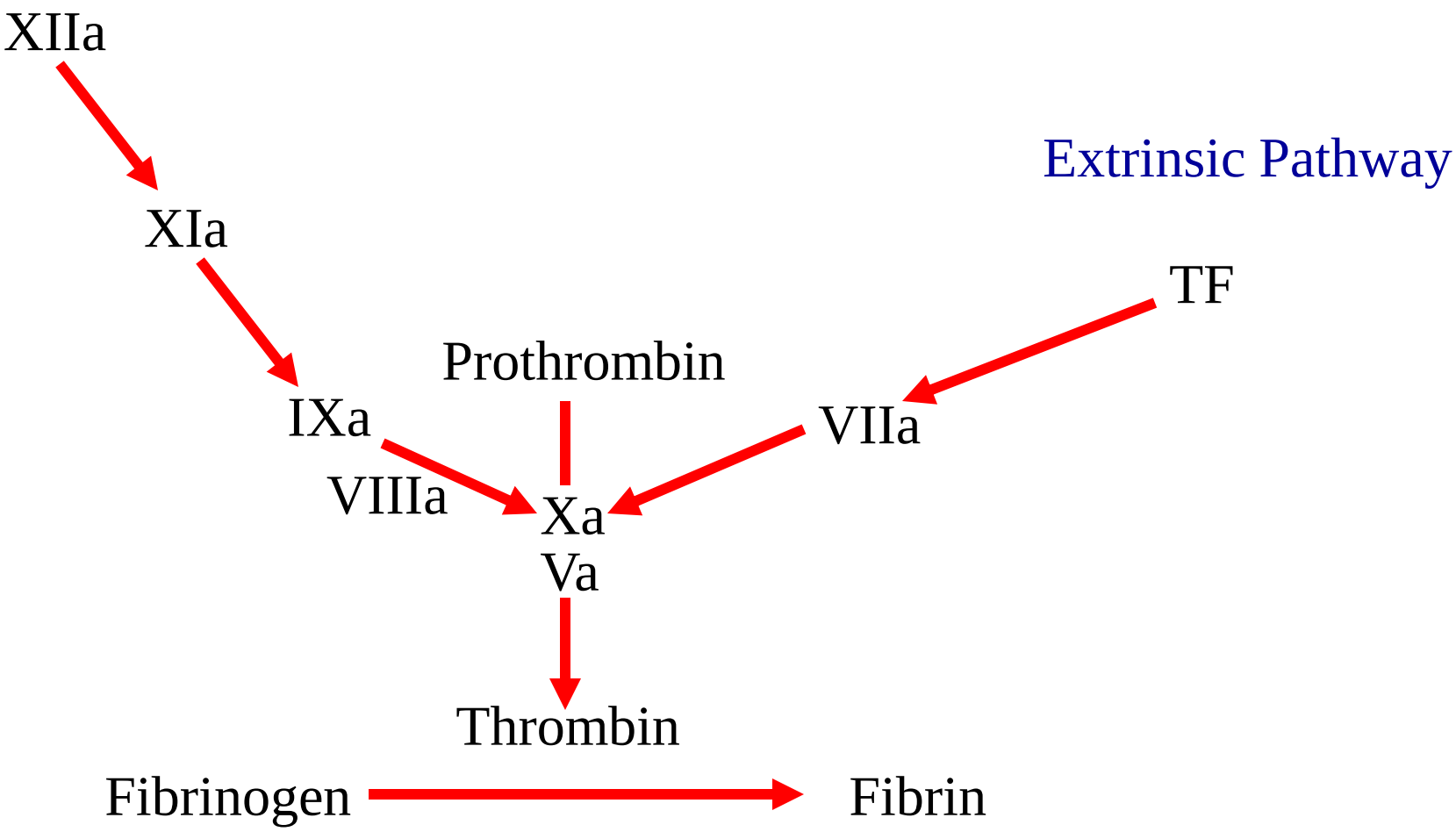

Fibrinogen
Fibrin


Thrombin
Fibrinogen
Fibrin

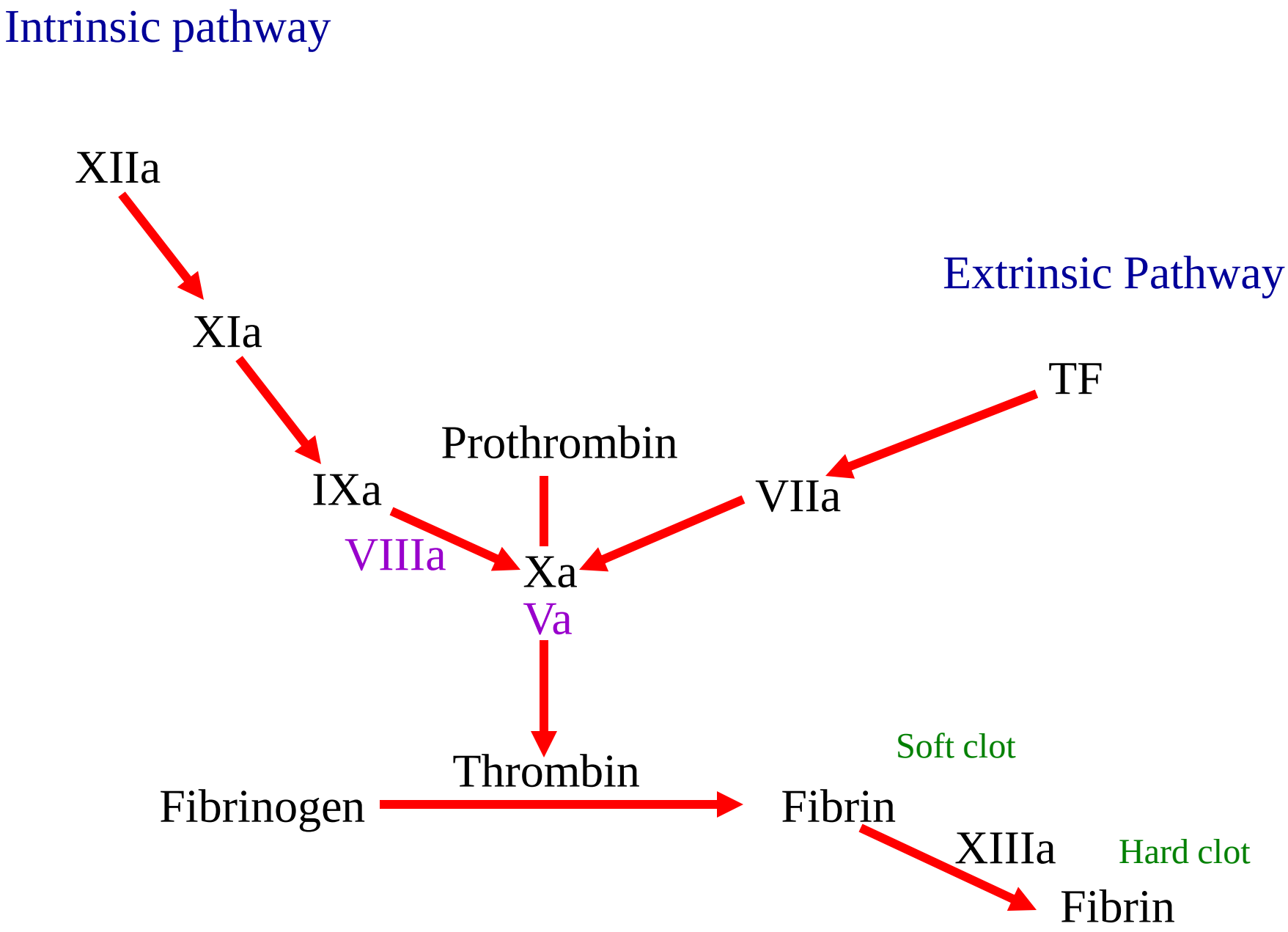

Prothrombin
Xa
Va
Thrombin
Fibrinogen
Fibrin


Extrinsic Pathway
TF
Prothrombin
VIIa
Xa
Va
Thrombin
Fibrinogen
Fibrin

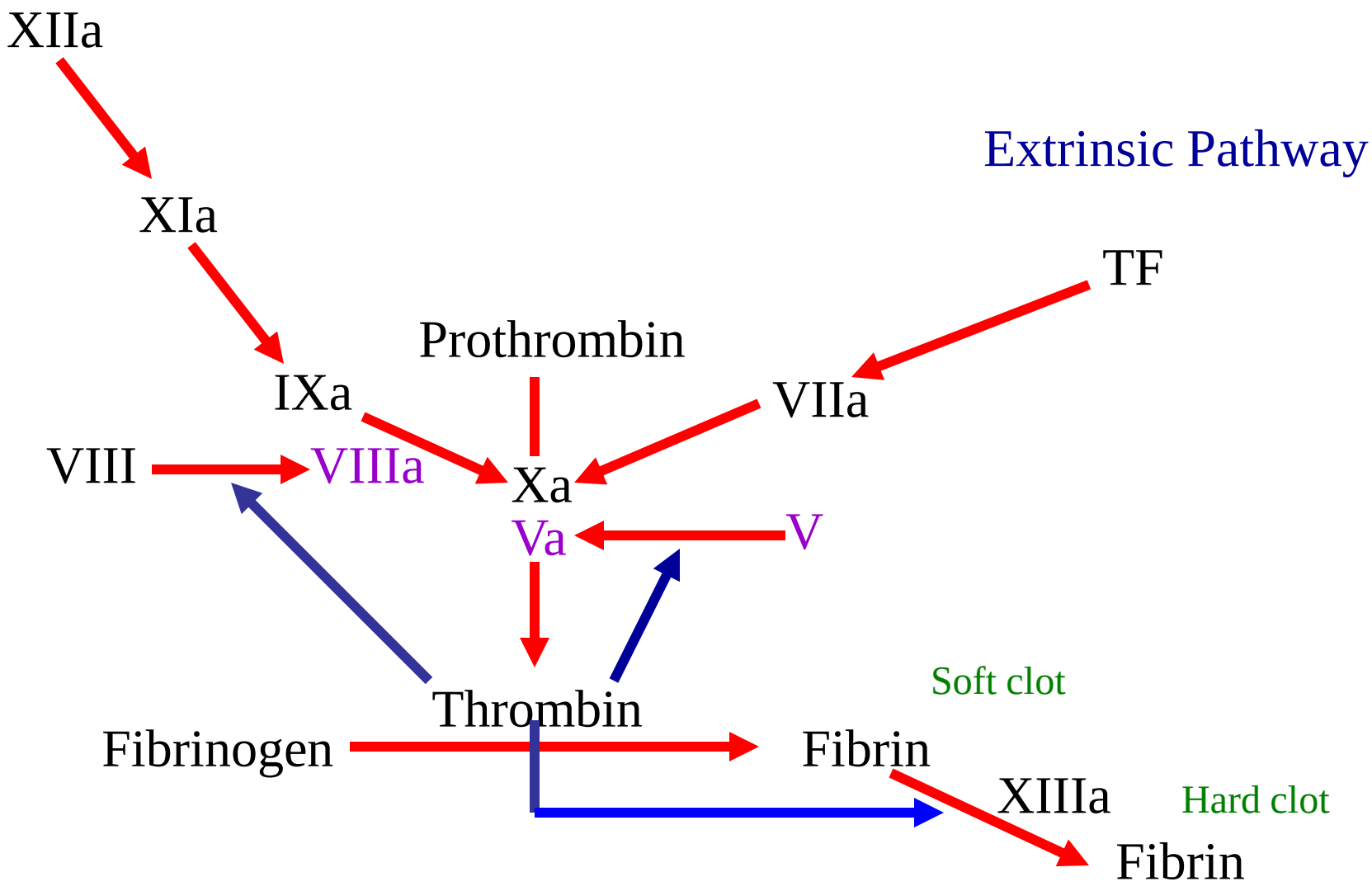
Intrinsic pathway



Extrinsic Pathway


Intrinsic pathway
XIIa
XIa
IXa
VIIIa
Prothrombin
Xa
Va
Extrinsic Pathway
TF
VIIa
Thrombin
Fibrinogen
Fibrin
Soft clot
XIIIa
Hard clot
Fibrin

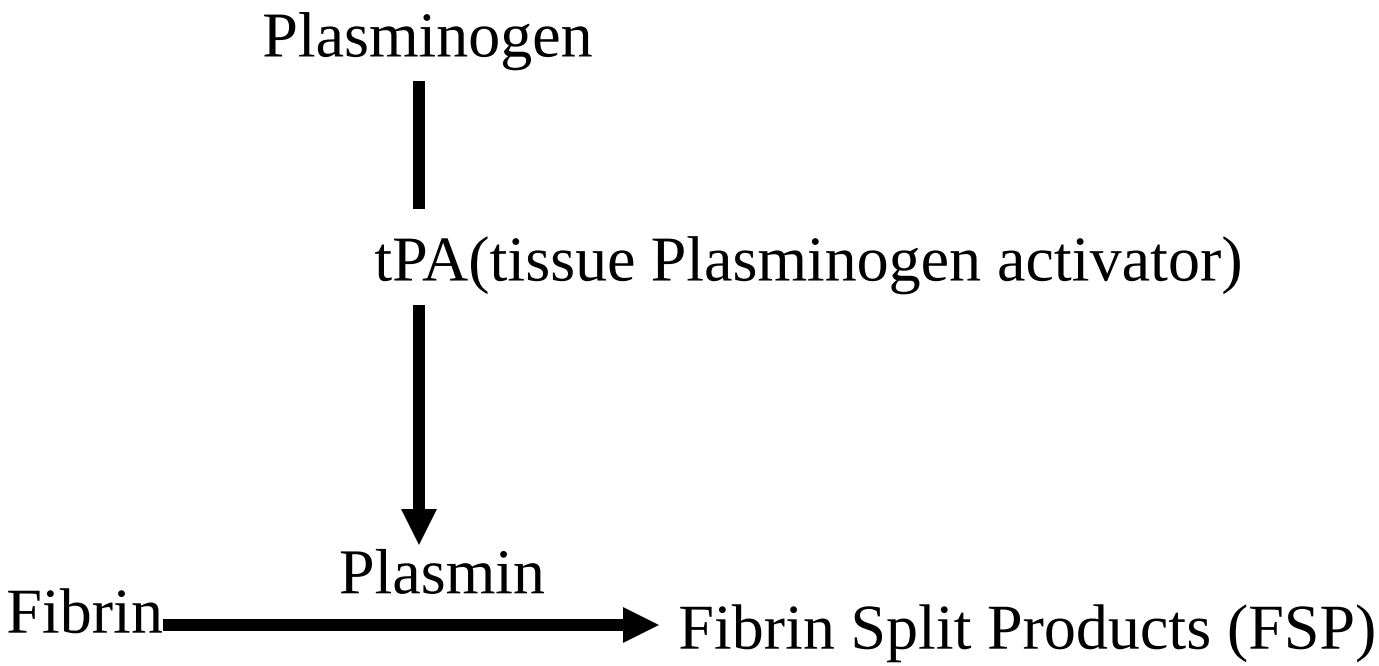
Intrinsic pathway



Clot removal

Fibrinolysis

Fibrinolysis



Inhibitors of fibrinolysis

- **Plasminogen activator inhibitors (PAIs)**

- **α_2-antiplasmin (serpin)**

Tests of Haemostatic function- summary

Screening tests	Abnormalities indicated by prolongation	Most common cause of disorder
Thrombin time (TT)	Deficiency or abnormality of fibrinogen or inhibition of thrombin by heparin or FDPs	Disseminated intravascular coagulation Heparin therapy
Prothrombin time (PT)	Deficiency or inhibition of one or more of the following coagulation factors: VII, X, V, II, fibrinogen	Liver disease Warfarin therapy DIC
Activated partial thromboplastin time (APTT or PTTK)	Deficiency or inhibition of one or more of the following coagulation factors: XII, XI, IX (Christmas disease), VIII (haemophilia), X, V, II, fibrinogen	Haemophilia, Christmas disease (+ conditions above)
Fibrinogen quantitation	Fibrinogen deficiency	Disseminated intravascular coagulation, liver disease

Tests for platelets abnormality

Platelet tests:

1)Platelet Count

2)Platelet function:

- Aggregation
- Flow cytometry