Haemostasis

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

1. Recognize different stages of hemostasis
2. Describe formation and development of platelet
3. Describe the role of platelets in hemostasis.
4. Recognize different clotting factors
5. Describe the cascade of clotting .

5. Describe the cascade of intrinsic pathway.
6. Describe the cascade of extrinsic and common pathways.
7. Recognize the role of thrombin in coagulation
8. Recognize process of fibrinolysis and function of plasmin

Haemostasis or Hemostasis

NOT

Homeostasis

The ability to maintain a constant internal environment in response to environmental changes

Hemostasis:

the spontaneous arrest of bleeding from ruptured blood vessels

Mechanisms:

1. Vessel wall
2. Platelet
3. Blood coagulation
4. Fibrinolytic system

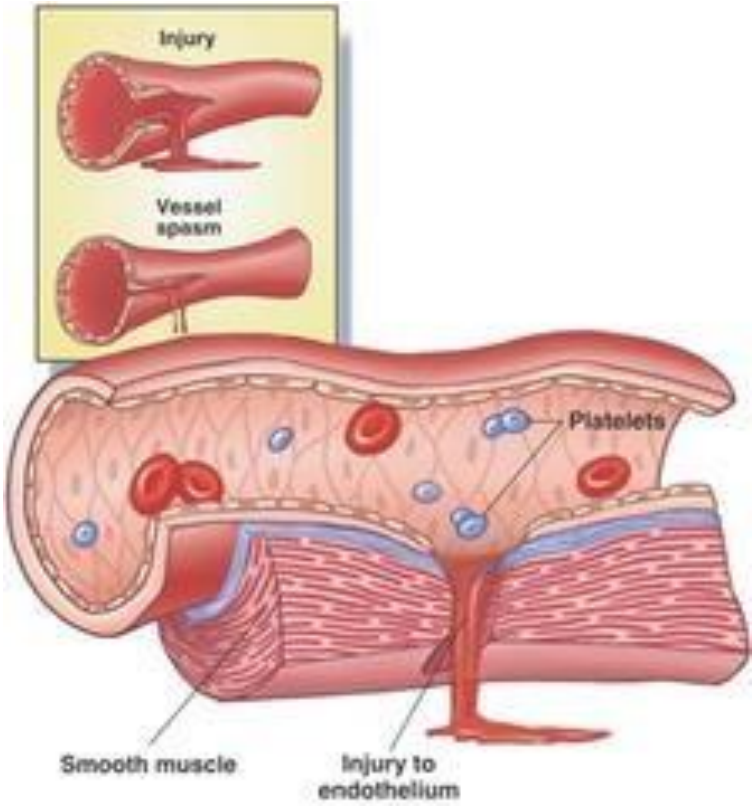
Hemostatic Mechanisms- cont

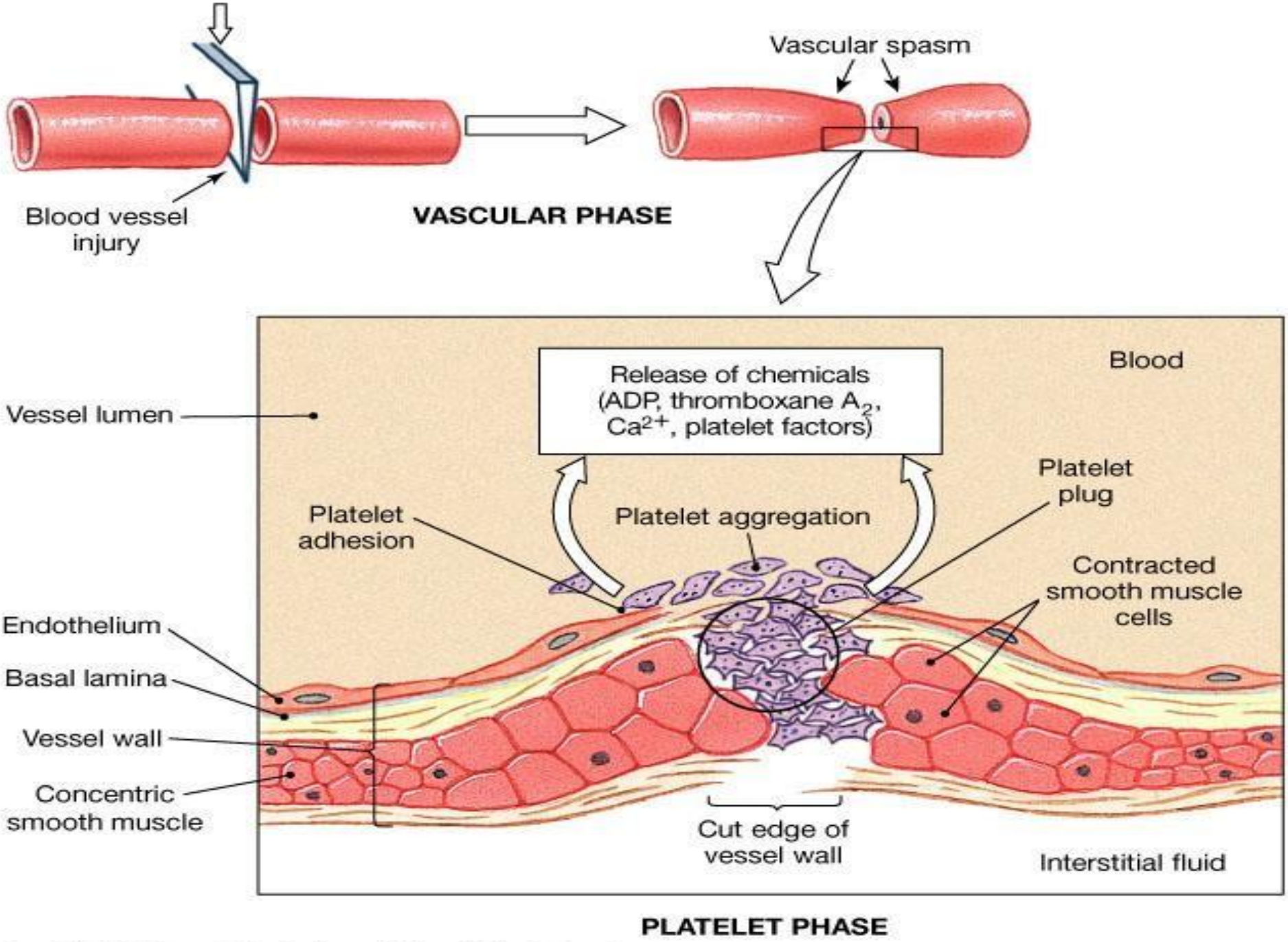
1 .Vessel wall

- Immediately After injury a localized

Vasoconstriction

- Mechanism:
  - Systemic release of adrenaline
  - Nervous factors
  - local release of thromboxane A2 & 5HT by platelets



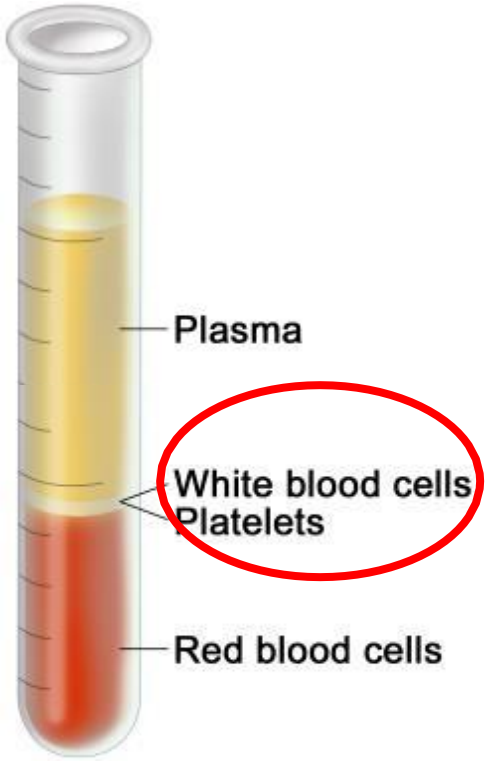


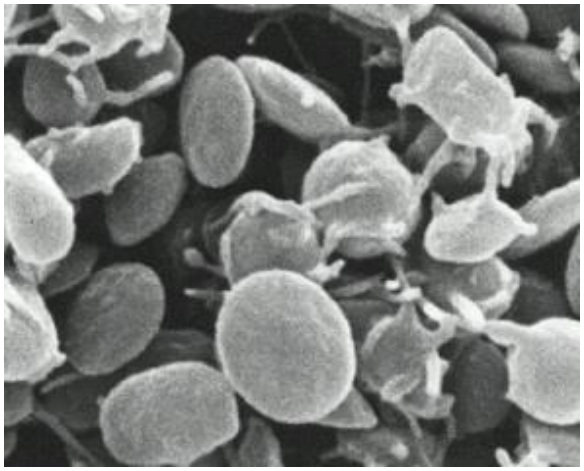
Hemostatic Mechanisms:

- Mechanisms:
  - Vessel wall
  - Platelet
  - Blood coagulation
  - Fibrinolytic system

Platelets (PLT)

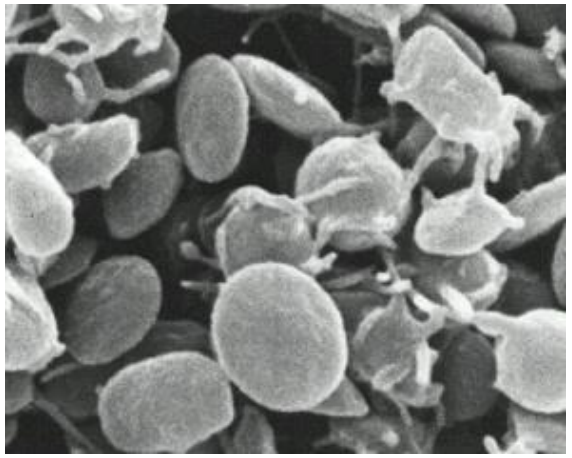
Thrombocytes

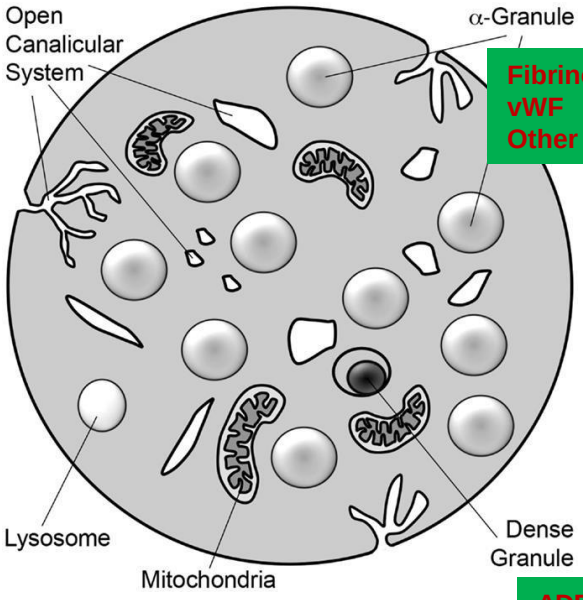


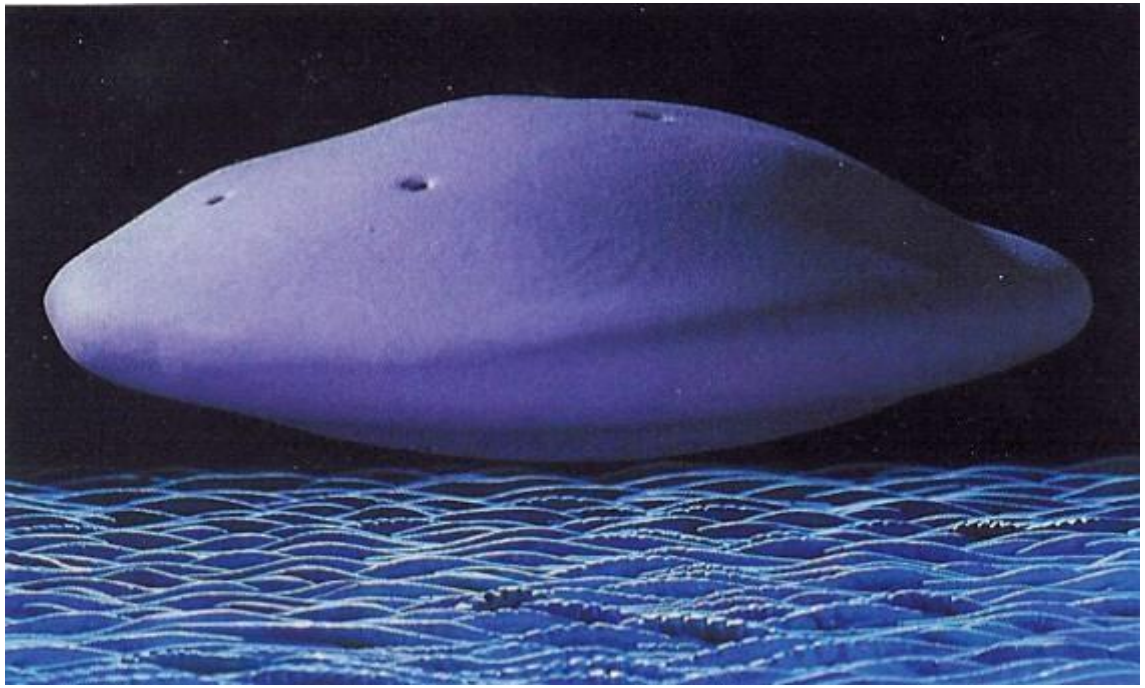


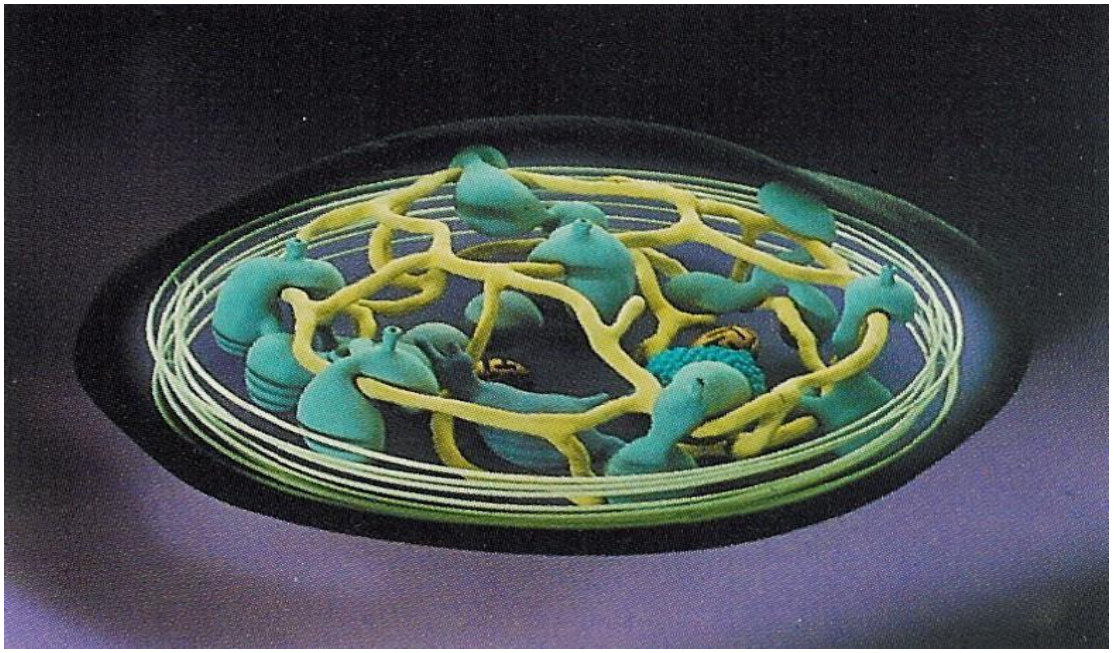
Platelets - cont

- small disc shaped cells
- Platelet count = $150x10^3$-$300x10^3$/ml,
- life span 8-12 days
- Contain high calcium content & rich in ADP
- Active cells contain contractile protein,

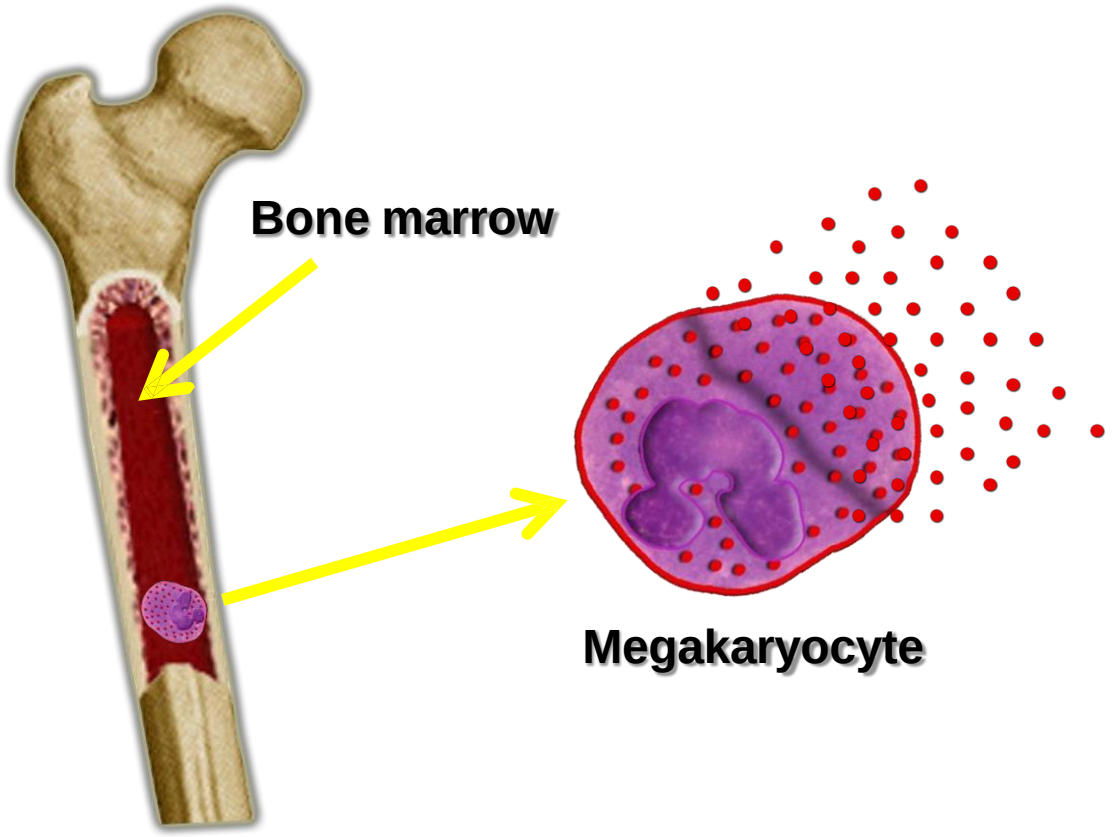








platelets



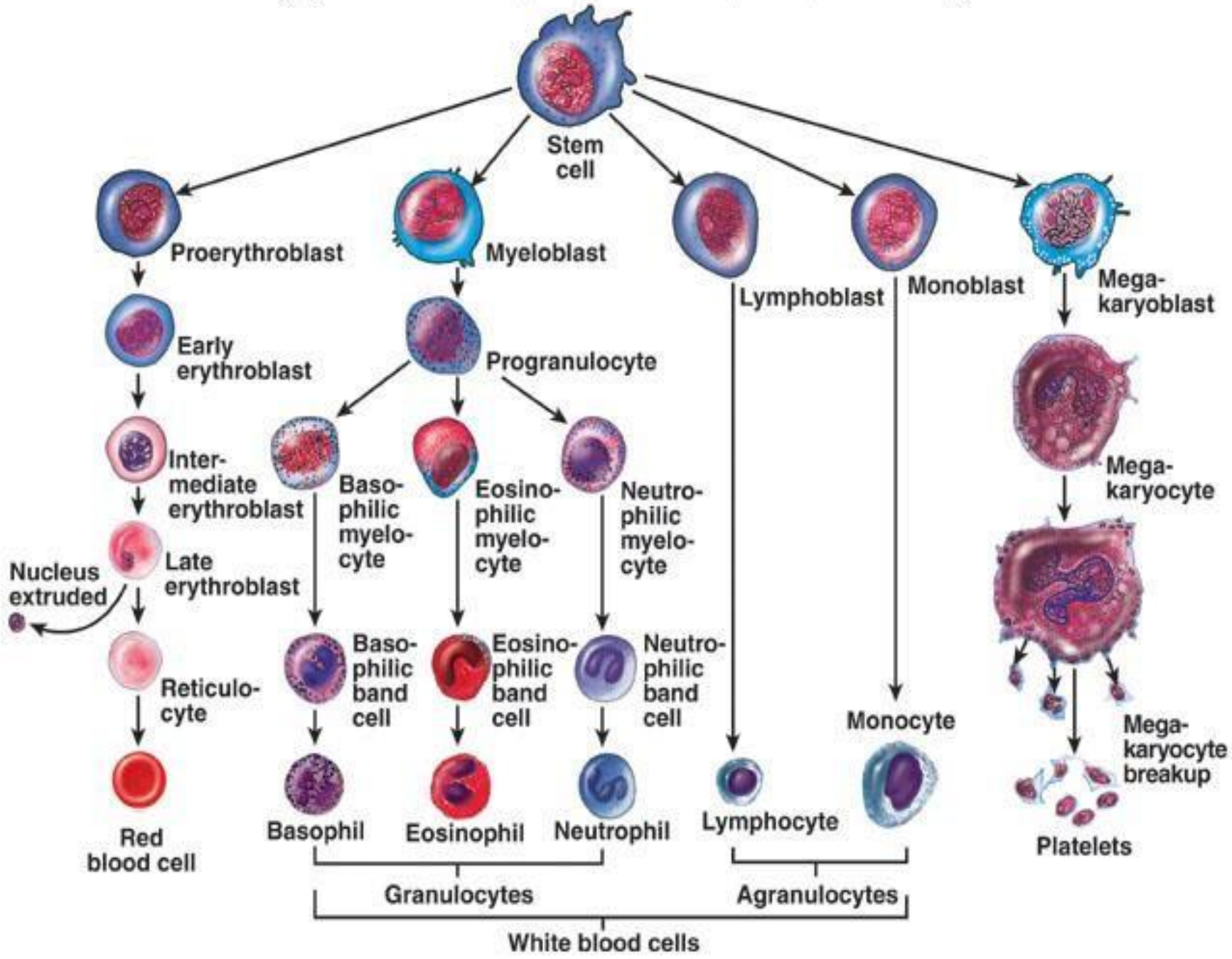
- Thrombocytes are

Fragments of megakaryocytes in the bone marrow

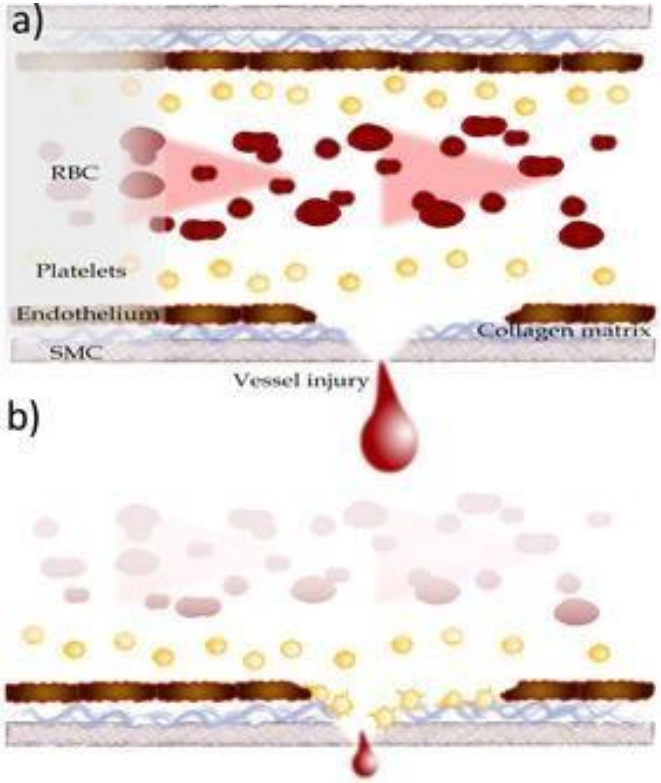
- Regulation of thrombopoiesis

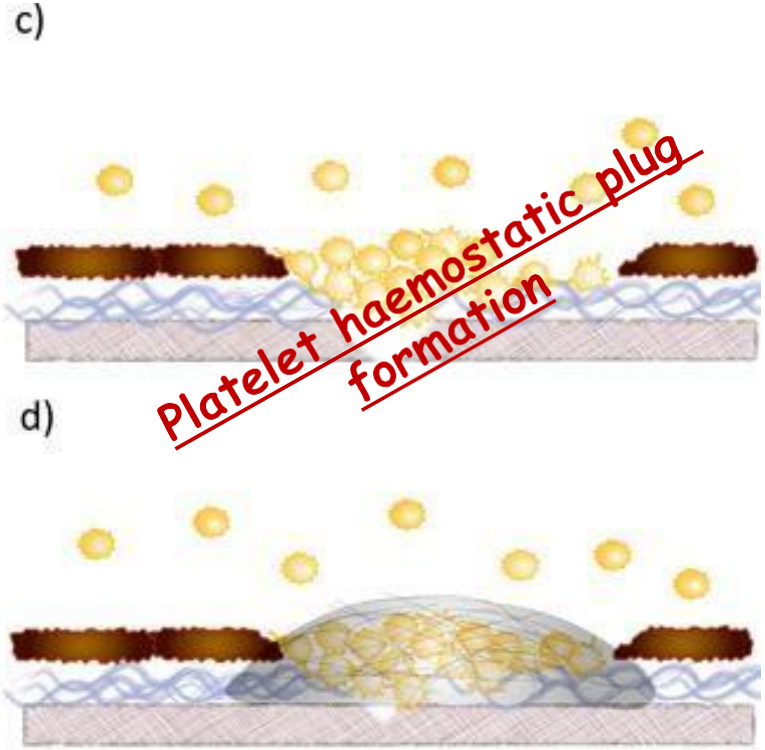
By:

Thrombombopoietin



Platelet haemostatic plug formation





Platelet Functions

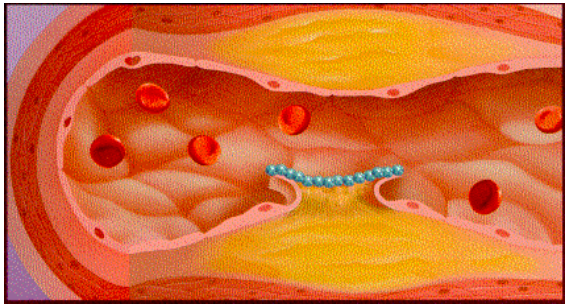
Begins with Platelet activation

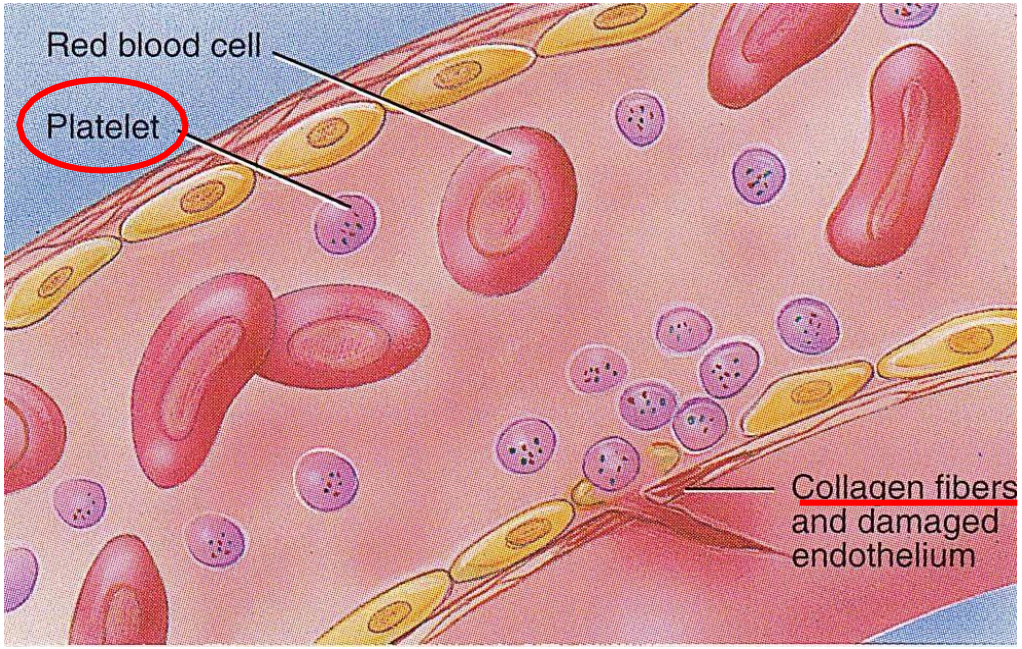
Platelet Activation

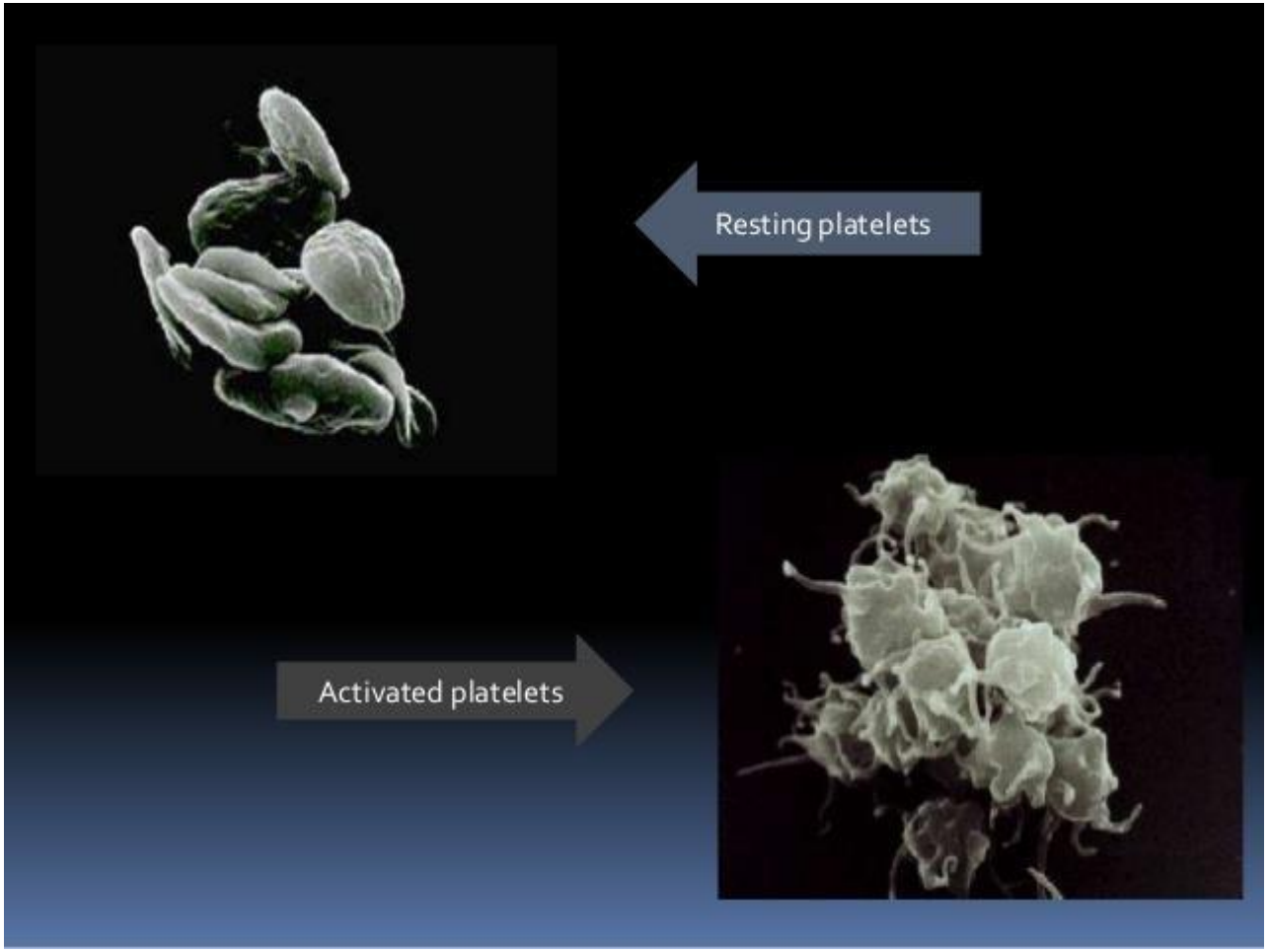
- Adhesion
- Shape change
- Aggregation
- Release
- Clot Retraction

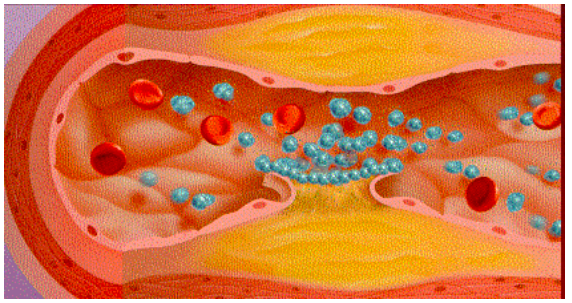
Platelet Adhesion

- Exposed collagen attracts platelets
- Platelets stick to exposed collagen underlying damaged endothelial cells in vessel wall





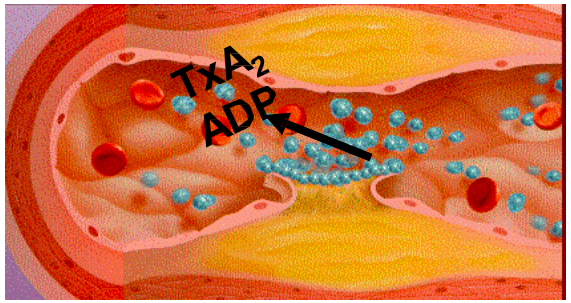




- **Platelets activated by adhesion**
- **Extend projections to make contact with each other**

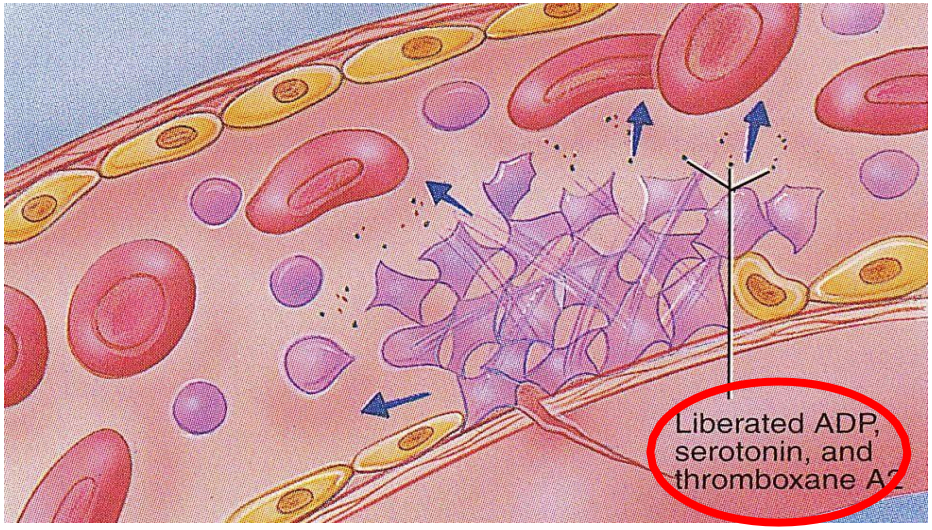
Platelet Release Reaction

•Activated platelets release Serotonin, ADP & Thromboxane A2



- **Serotonin & thromboxane A2 are vasoconstrictors decreasing blood flow through the injured vessel.**

- **ADP & Thromboxane A2 (TXA2) → ↑ the stickiness of platelets → ↑ Platelets aggregation → plugging of the cut vessel**



Activated Platelets

Secrete:

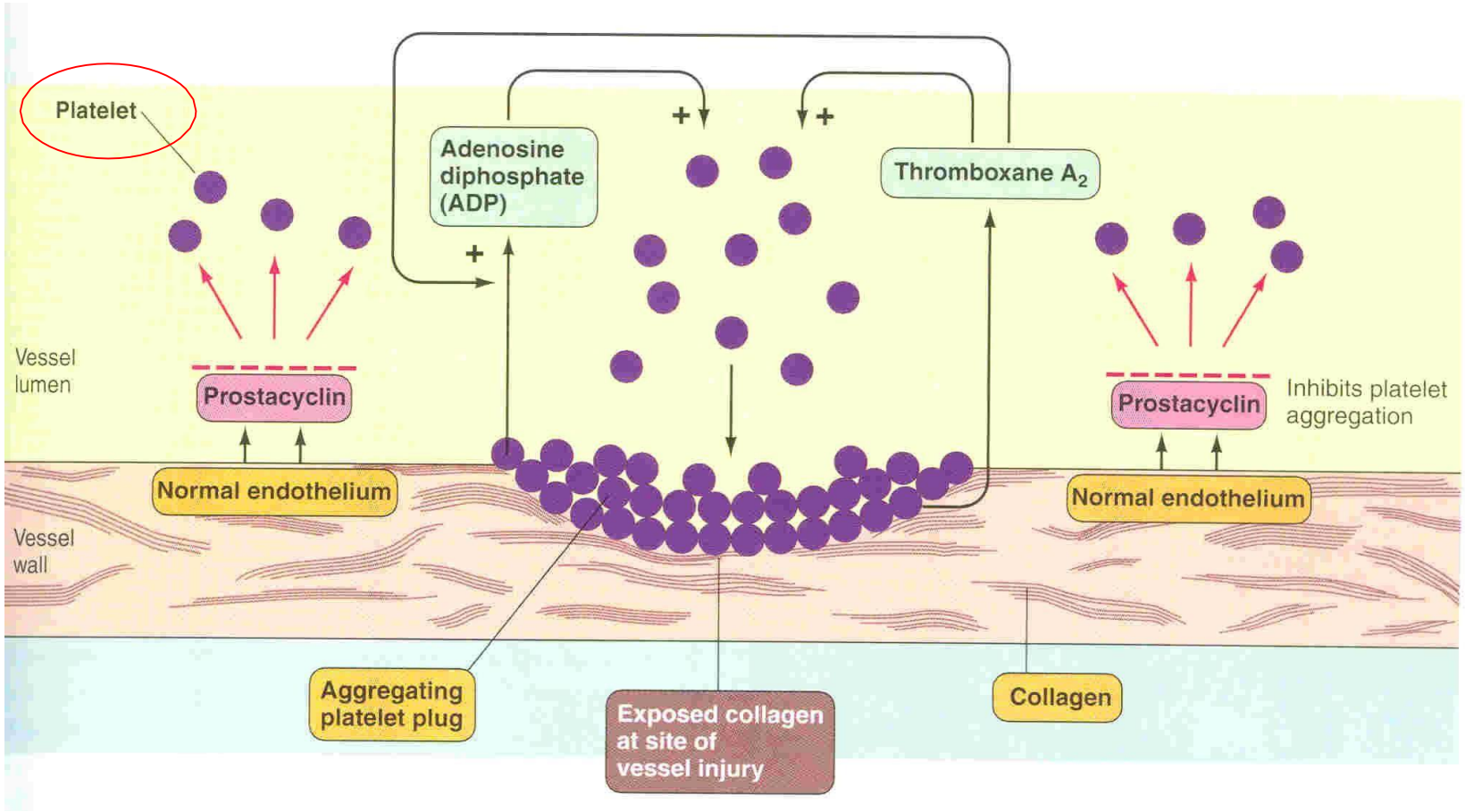
1. 5HT →vasoconstriction
2. ADP
3. Platelet phospholipid (PF3) → clot formation
4. Thromboxane A2 (TXA2) is a prostaglandin formed from arachidonic acid

   Function:

   - vasoconstriction
   - Platelet aggregation

   (TXA2 inhibited by aspirin)

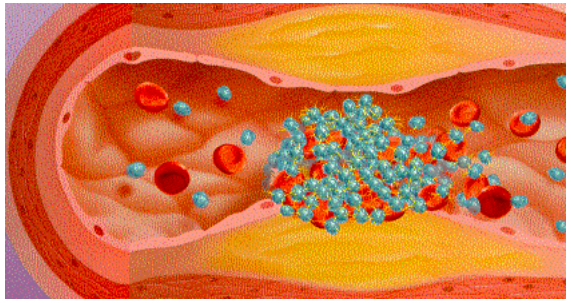
Platelets aggregation



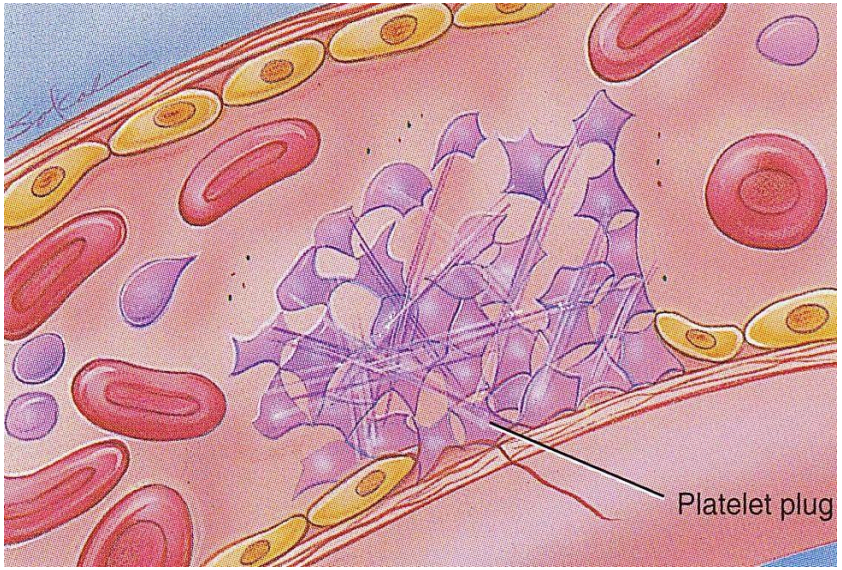
- **Intact endothelium secret prostacyclin and NO which inhibit aggregation**

Platelet Aggregation

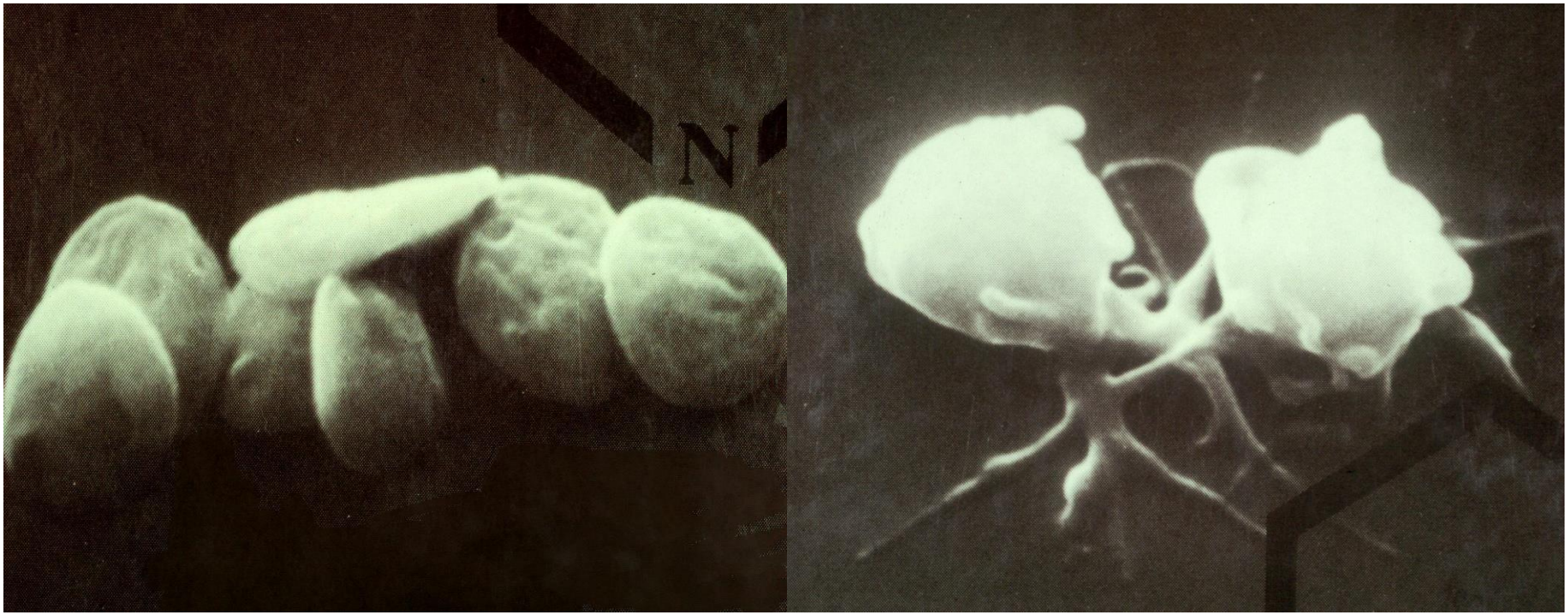
- **Activated platelets stick together and activate new platelets to form a mass called a platelet plug**



- **Plug reinforced by fibrin threads formed during clotting process**



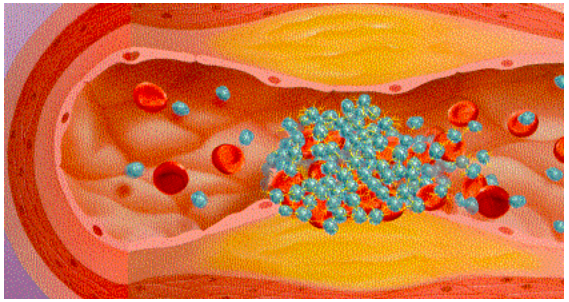
Platelet shape change and Aggregation

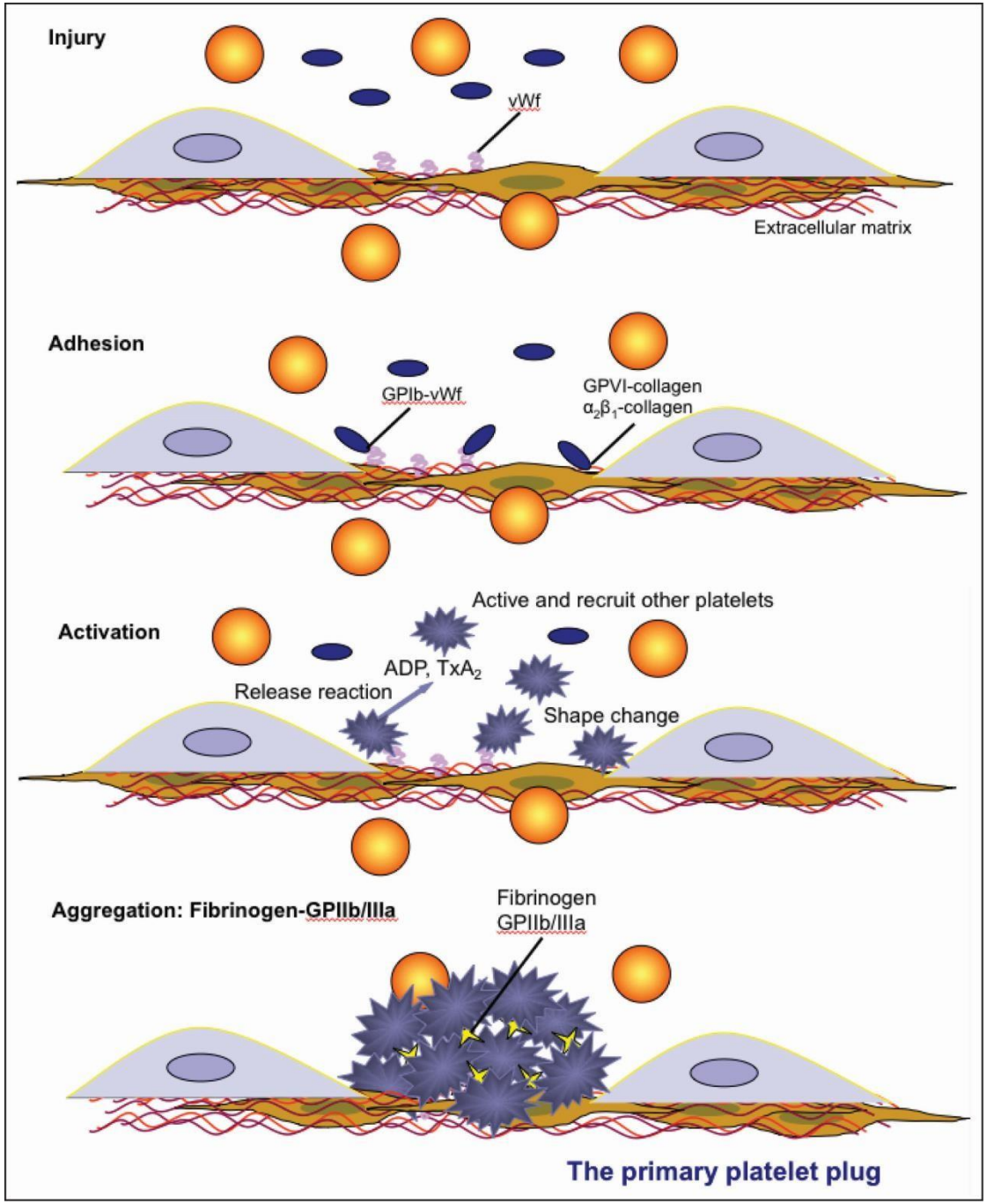


Platelet Activation

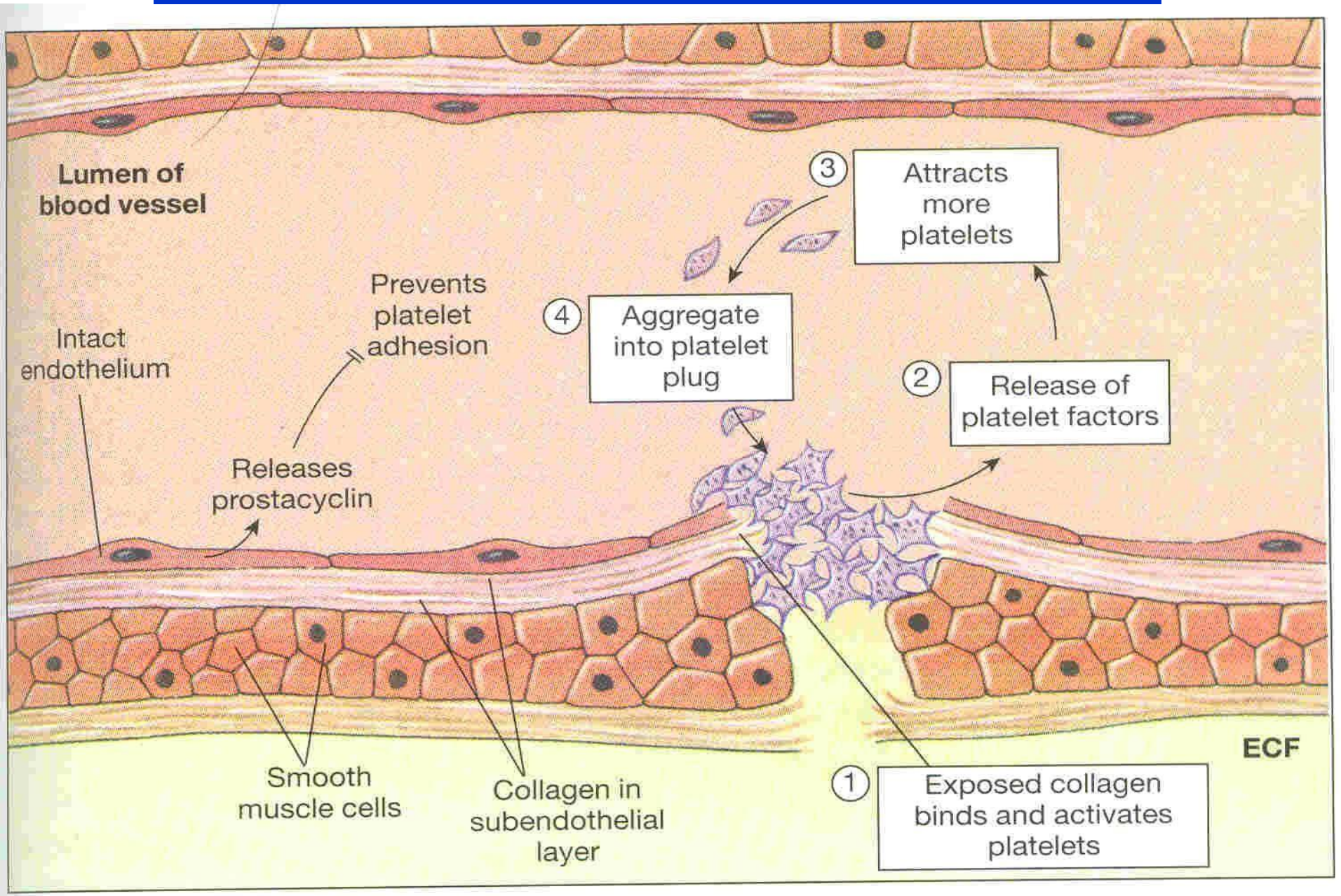
- **Clot Retraction**:

  Myosin and actin filaments in platelets are stimulated to contract during aggregation further reinforcing the plug and help release of granule contents




Injury
vWf
Extracellular matrix
Adhesion
GPIb-vWf
GPVI-collagen
$\alpha_2\beta_1$-collagen
Activation
Active and recruit other platelets
ADP, TxA_2
Release reaction
Shape change
Aggregation: Fibrinogen-GPIIb/IIIa
Fibrinogen
GPIIb/IIIa
The primary platelet plug

Platelet plug formation



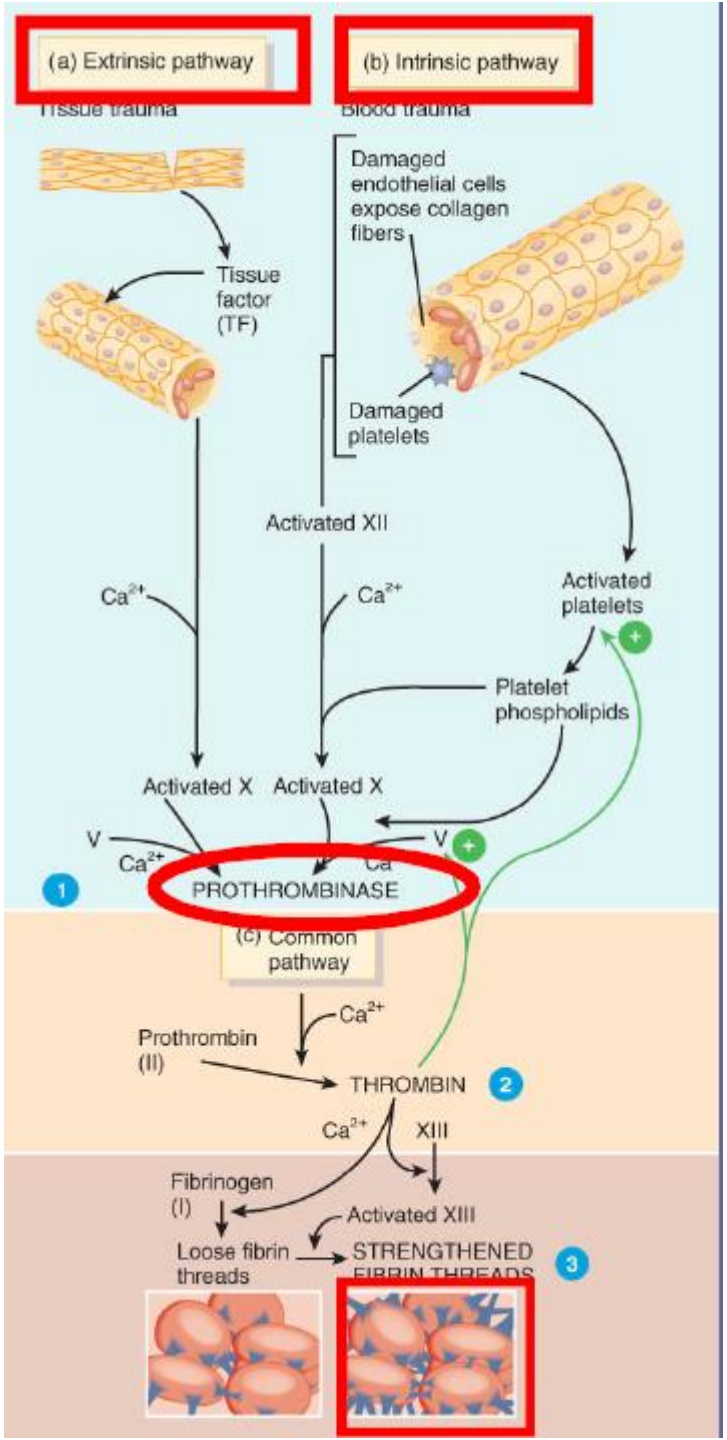
Memostatic Mechanisms:

- Mechanisms:
  - Vessel wall
  - Platelet
  - Blood coagulation
  - Fibrinolytic system

Blood Clotting

Clotting is a cascade of reactions in which each clotting factor activates the next in a fixed sequence resulting in the formation of fibrin threads

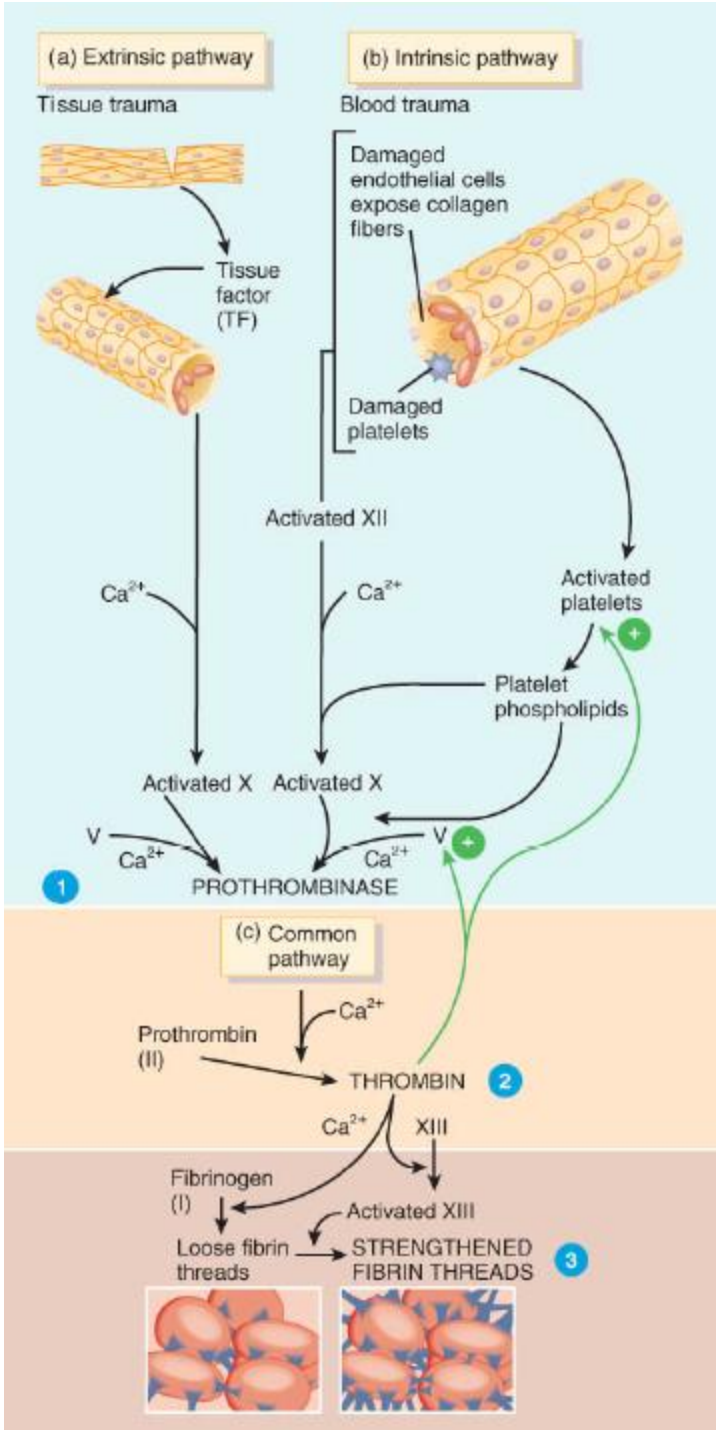
- prothrombinase & Ca^{+2} convert prothrombin into thrombin
- thrombin converts fibrinogen into fibrin threads



Overview of the Clotting Cascade

Prothrombinase is formed by either the intrinsic or extrinsic pathway

Final common pathway produces fibrin threads



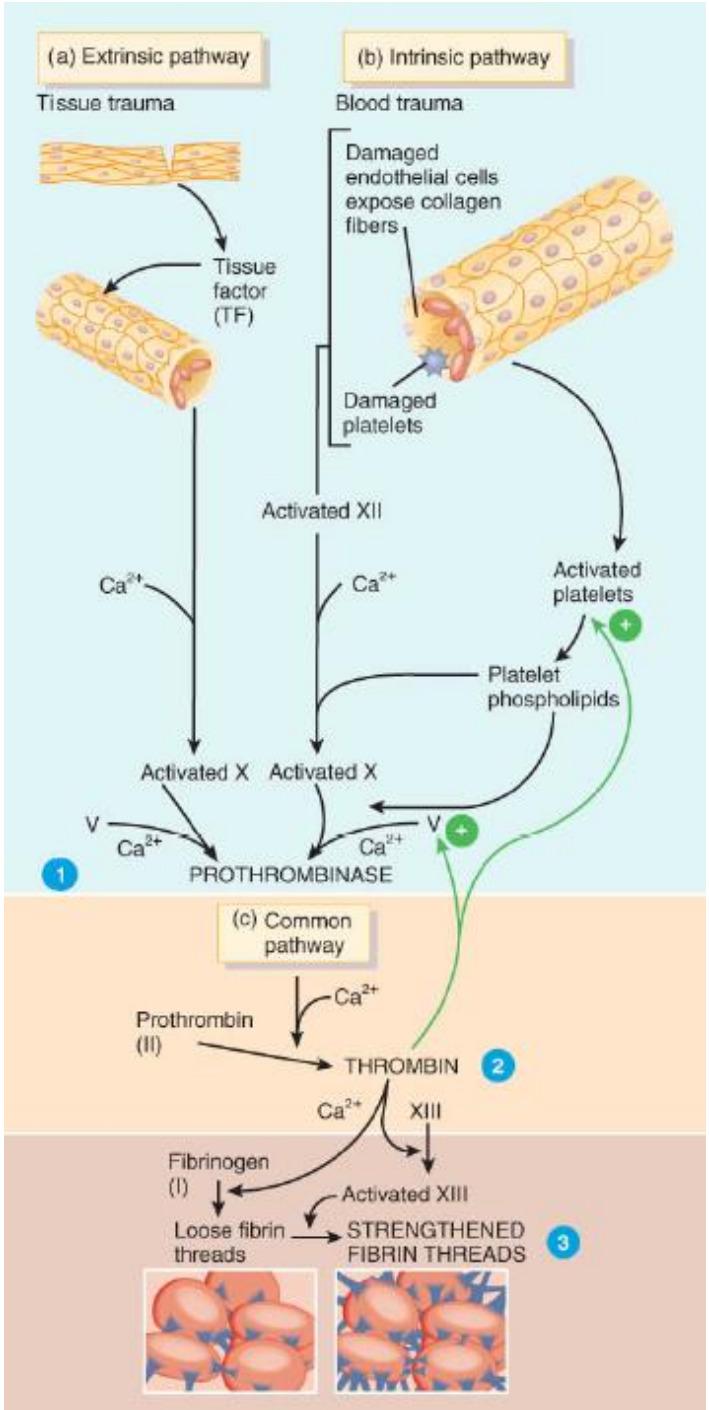
Extrinsic Pathway

Damaged tissues leak tissue factor (thromboplastin) into bloodstream

Prothrombinase forms in seconds

In the presence of Ca^{+2}, clotting factor X combines with V to form prothrombinase

Intrinsic Pathway

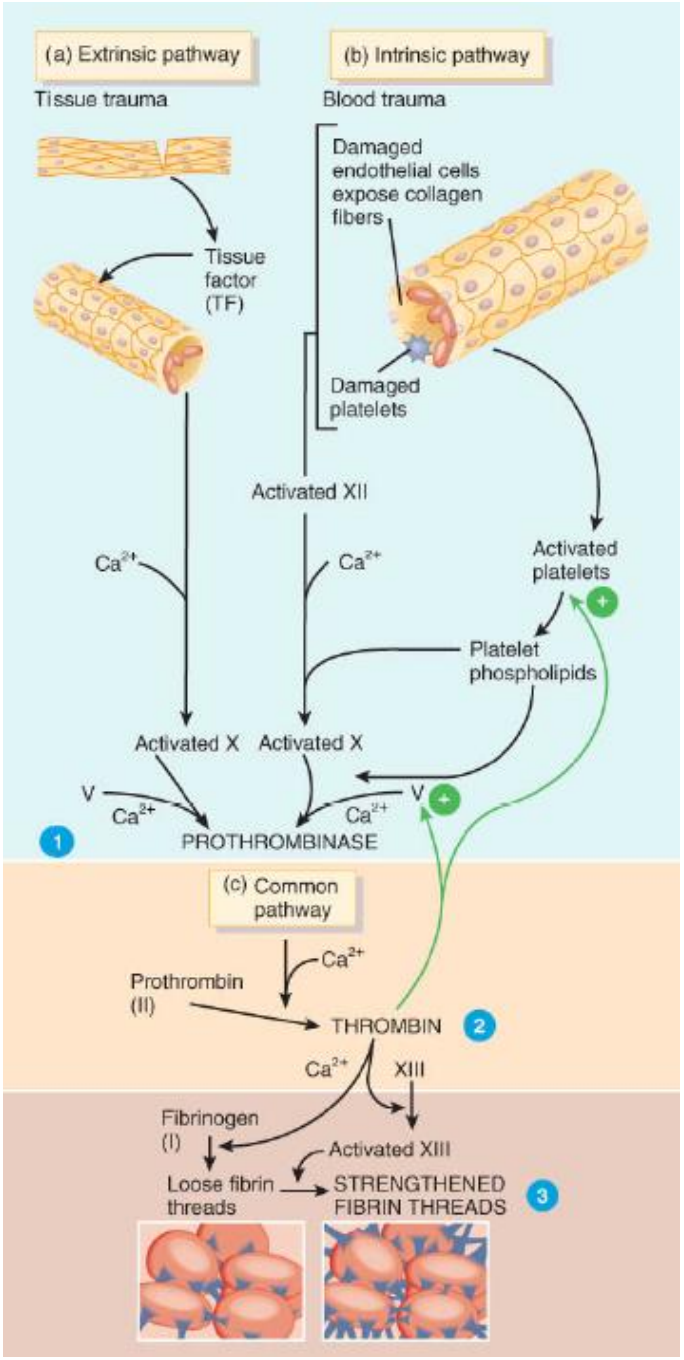


Activation occurs

- endothelium is damaged & platelets come in contact with collagen of blood vessel wall
- platelets damaged & release phospholipids

Requires several minutes for reaction to occur

Substances involved: Ca^{+2} and clotting factors XII, X and V



Final Common Pathway

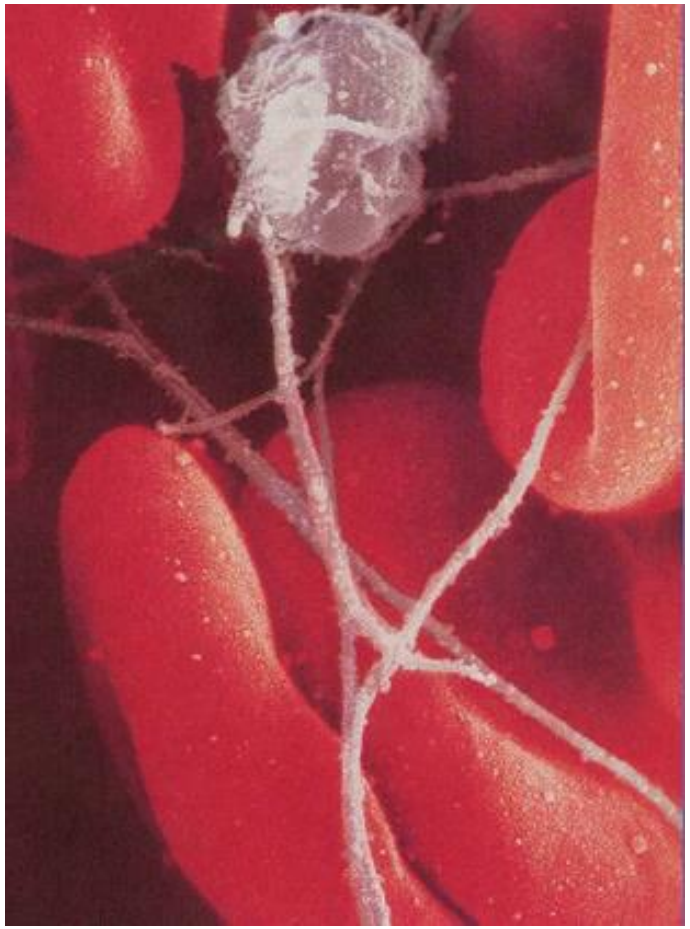
Prothrombinase and Ca^{+2}

- catalyze the conversion of prothrombin to thrombin

Thrombin

- in the presence of Ca^{+2} converts soluble fibrinogen to insoluble fibrin threads
- activates fibrin stabilizing factor XIII
- positive feedback effects of thrombin
- accelerates formation of prothrombinase
- activates platelets to release phospholipids

Clot Retraction & Blood Vessel Repair



Clot plugs ruptured area of blood vessel

Platelets pull on fibrin threads causing clot retraction

- trapped platelets release factor XIII stabilizing the fibrin threads

Edges of damaged vessel are pulled together

Fibroblasts & endothelial cells repair the blood vessel

Role of Vitamin K in Clotting

Normal clotting requires adequate vitamin K

- fat soluble vitamin absorbed if lipids are present
- absorption slowed if bile release is insufficient

Required for synthesis of 4 clotting factors by hepatocytes

- factors II (prothrombin), VII, IX and X (1972)

Produced by bacteria in large intestine

Hemostasis:

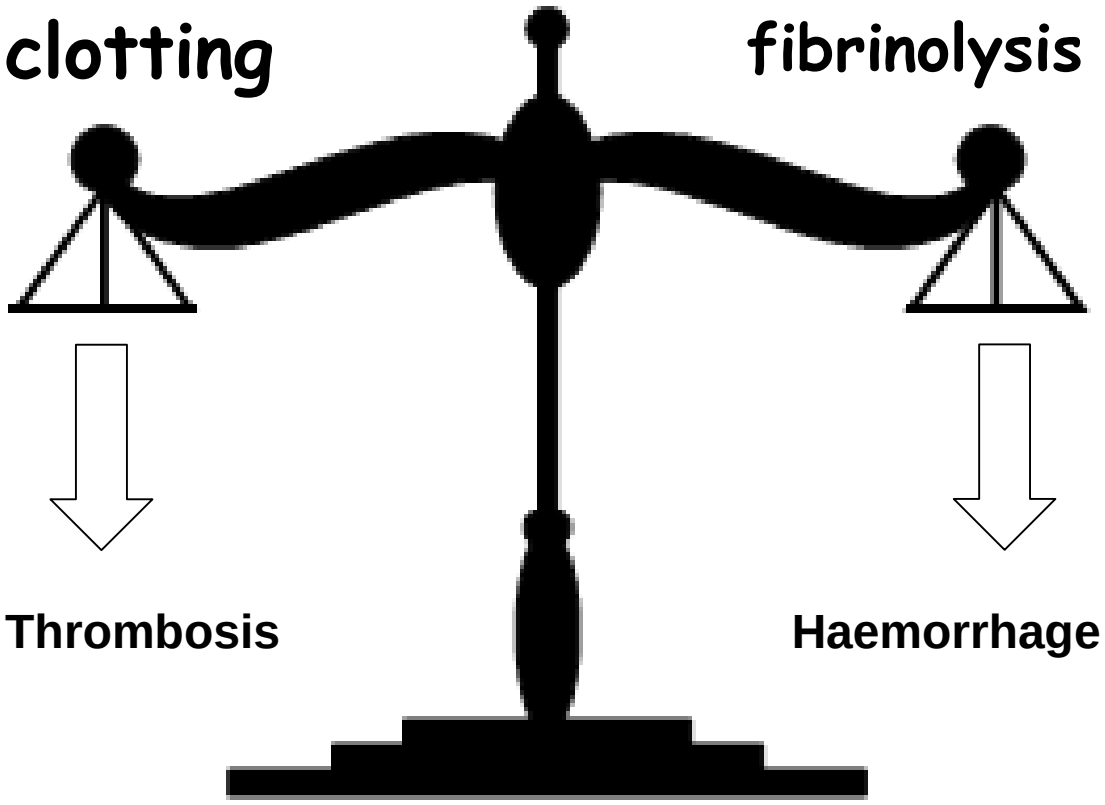
the spontaneous arrest of bleeding from ruptured blood vessels

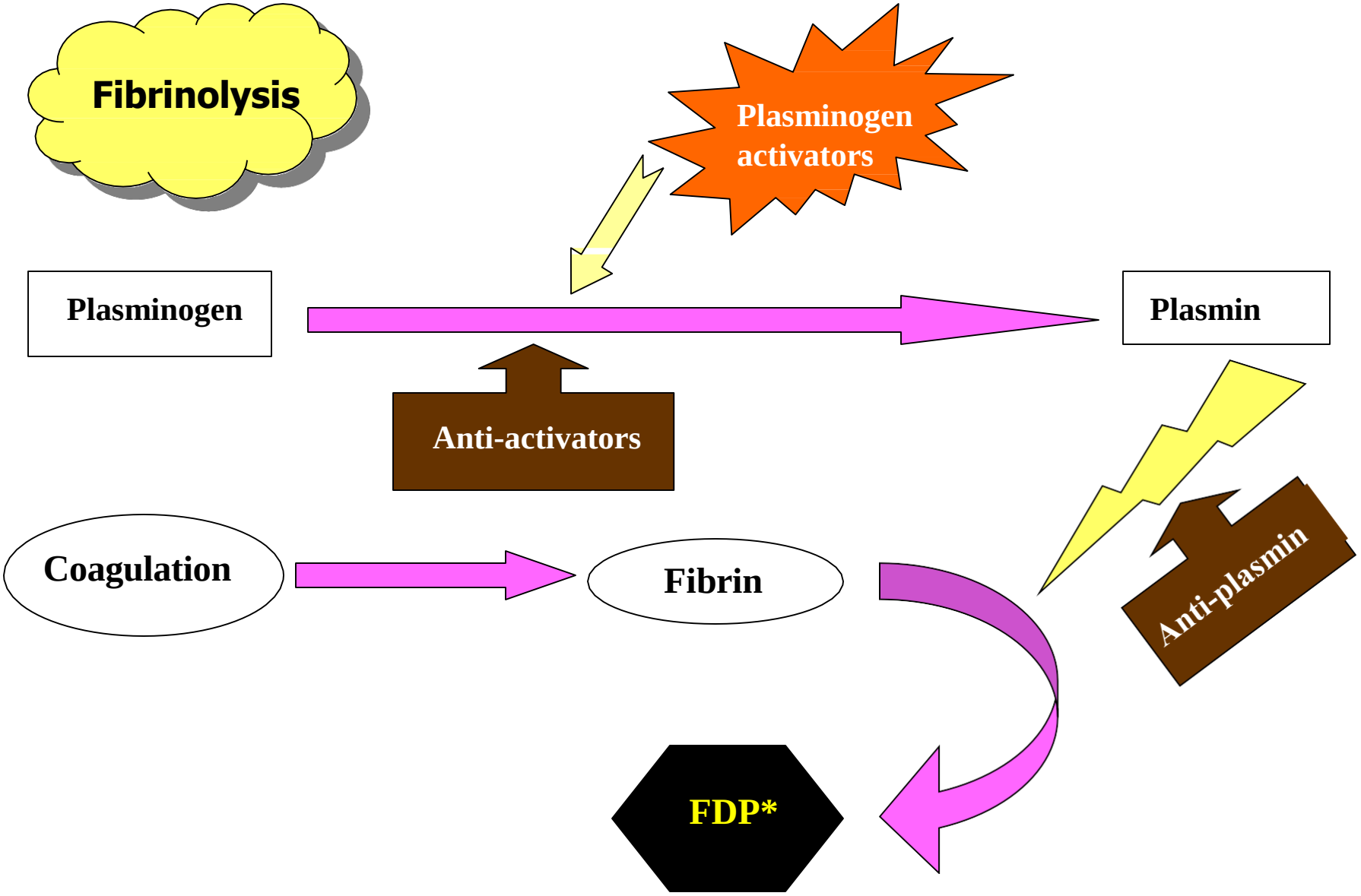
Mechanisms:

1. Vessel wall
2. Platelet
3. Blood coagulation
4. Fibrinolytic system (Fibrinolysis)

Fibrinolysis

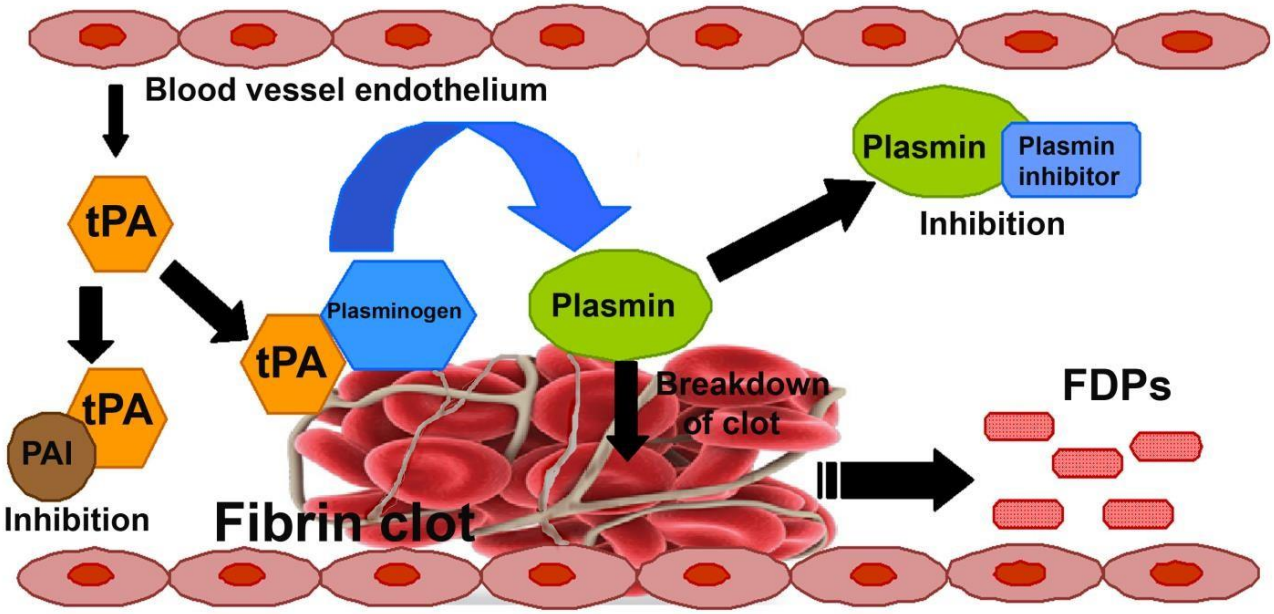
- Formed blood clot can either become fibrous or dissolve
- Fibrinolysis (dissolving) = Break down of fibrin by naturally occurring enzyme plasmin therefore prevent intravascular blocking
- There is balance between clotting and fibrinolysis
  - Excess clotting →blocking of Blood Vessels
  - Excess fibrinolysis →tendency for bleeding


clotting
fibrinolysis
Thrombosis
Haemorrhage

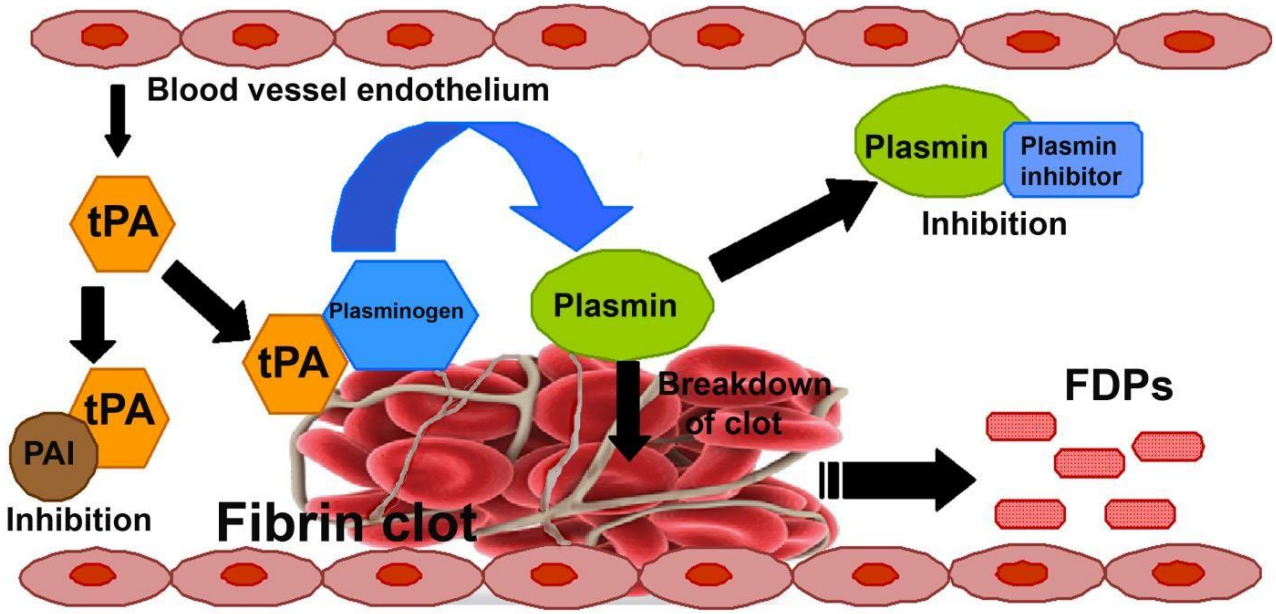


The fibrinolytic System

FDP*: Fibrin Degradation Products

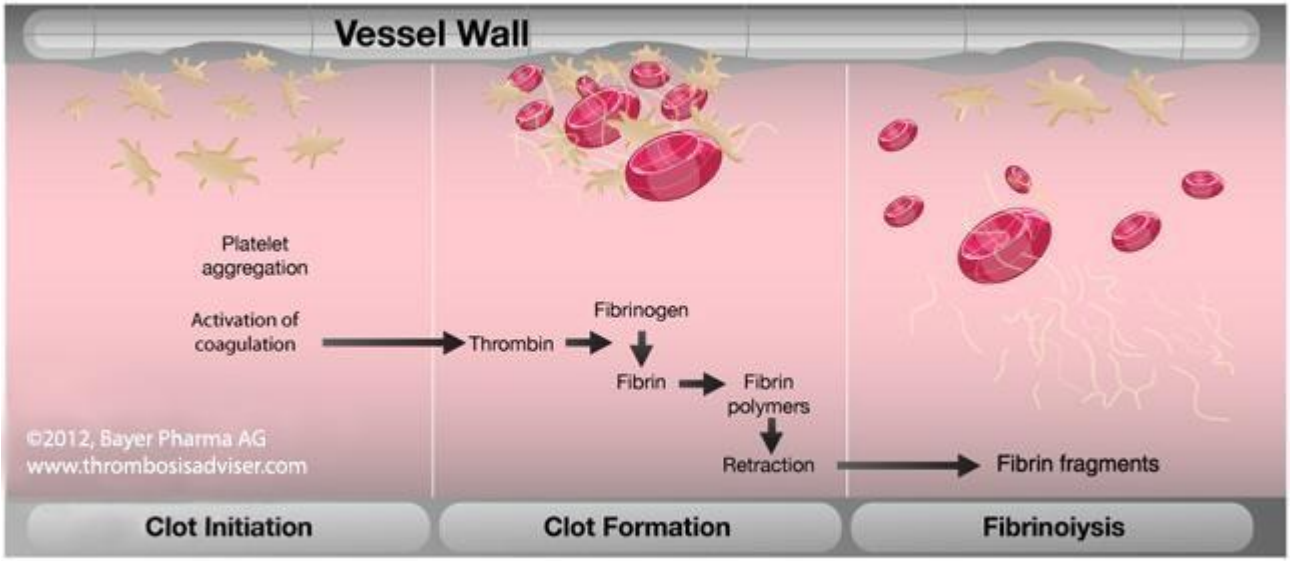


- Plasmin is present in the blood in inactive form plasminogen
- Plasmin is activated by tissue plasminogen activators (t-PA) in blood.
- Plasmin digest intra & extra vascular deposit of Fibrin → fibrin degradation products (FDP)
- Unwanted effect of plasmin is the digestion of clotting factors

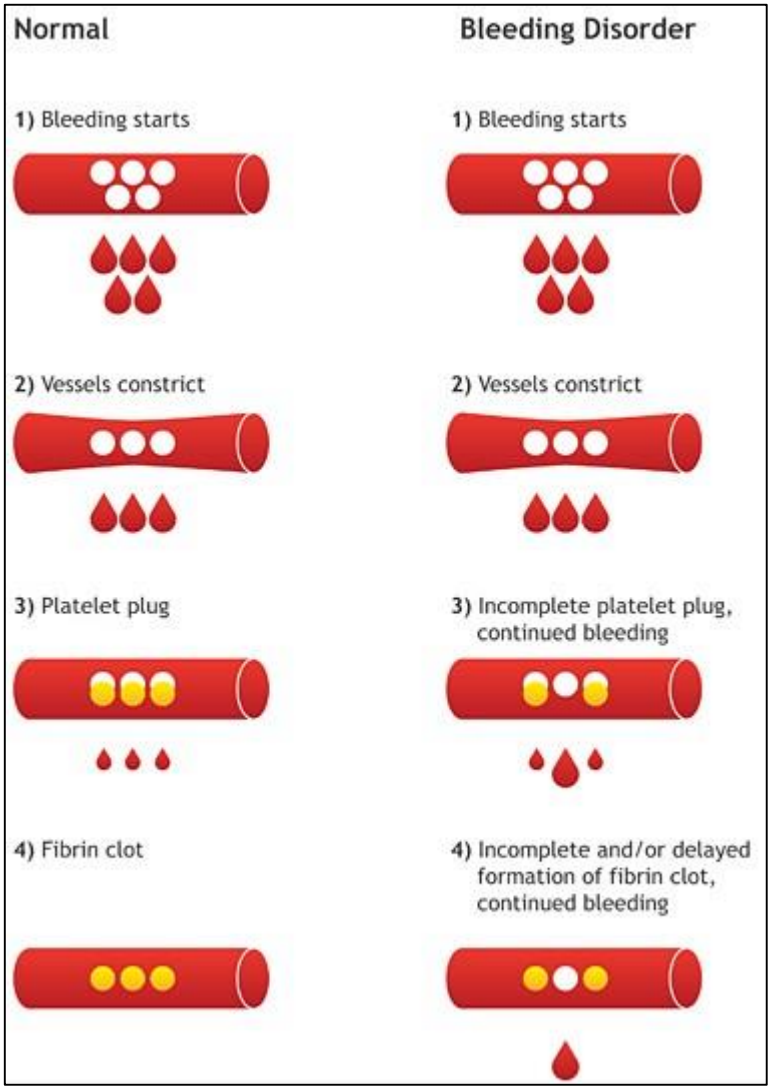


- Plasmin is controlled by:
  - Plasminogen Activator Inhibitor (PAI)
  - Antiplasmin from the liver
- Uses:
  - Tissue Plasminogen Activator (t-PA) used to activate plasminogen to dissolve coronary clots

Haemostatic Mechanisms



Bleeding disorders



- Excessive bleeding can result from:
  - Platelet defects: deficiency in number (thrombocytopenia) or defect in function.
  - Coagulation factors defect: Deficiency in coagulation factors (e.g. hemophilia).
  - Vitamin K deficiency.

Cont. bleeding disorders

- Hemophilia:
  - ↑ bleeding tendency.
  - X-linked disease.
  - Affects males.
  - 85% due to FVIII deficiency (hemophilia A), and 15% due to FIX deficiency (hemophilia B).

- Vitamin K deficiency & liver disease:
  - Almost all coagulation factors are synthesized in the liver.
  - Prothrombin, FVII, FIX, & FX require vitamin K for their synthesis.