Hemostasis and coagulation
Hemostasis

- Is a complex process which causes the bleeding process to stop
- Primary Hemostasis (Vessel wall, Platelets)
- Secondary Hemostasis (Coagulation Cascade)
3 Major systems involved

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

- **Vasoconstriction** of blood vessel.
- **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.
Exposed collagen binds and activates platelets.

Release of platelet factors

Attracts more platelets

Aggregate into platelet plug
A. VASOCONSTRICTION

- Endothelium
- Basement membrane
- Arteriole smooth muscle

Site of injury

Endothelin release causes vasoconstriction

Reflex vasoconstriction

ECM (collagen)
Platelets

• Produced in the bone marrow by fragmentation of the cytoplasm of megakaryocytes

• Synchronous replication: DNA replication in the absence of nuclear or cytoplasmic division
Megakaryocytes are giant cells with multiple copies of DNA in the nucleus.

The edges of the megakaryocyte break off to form cell fragments called platelets.
B. PRIMARY HEMOSTASIS

1. Platelet adhesion
2. Shape change
3. Granule release (ADP, TXA₂)
4. Recruitment
5. Aggregation (hemostatic plug)

Endothelium, basement membrane, collagen, vWF
C. SECONDARY HEMOSTASIS

1. Tissue factor
2. Phospholipid complex expression
3. Thrombin activation
4. Fibrin polymerization

Fibrin
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 hemostatic plug
Coagulation Factors

• 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 extrinsic Xase (TF, VIIa)
  2) The intrinsic Xase (IX, VIIIa)
  3) The above two enzymes generates the prothrombinase 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 (PF3), will activate prothrombin activator.
Coagulation process

• 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.
Clot removal

- Tissue plasminogen activator
- Urokinase plasminogen activator
- Plasminogen
- Kallikrein
- Plasmin
- Fibrinogen
- Fibrin
- Thrombin
- Fibrin degradation products

Nature Reviews | Molecular Cell Biology
• Plasminogen activator inhibitors (PAIs)
• $\alpha 2$-antiplasmin (serpin)