PHYSIOLOGY OF CLOT FORMATION

NOMPUMELELO JELE
HAEMOSTASIS

• Maintains the integrity of a closed, high-pressure circulatory system after vascular damage

• Vessel Wall Injury → events in the vessel wall and in the blood which seal breach

• Delicate balance exists between thrombogenesis and thrombolysis
PHASES OF HAEMOSTASIS

- Vascular Phase
  - Secretion of Endothelins will cause muscles to contract
  - Endothelial cells become “sticky”

- Platelet Phase
  - Activation of Platelets

- Coagulation Phase
  - Clotting Cascade
VESSEL WALL

• Inner Lining of Endothelium is crucial for Haemostasis

• Endothelial Thromboregulators:
  • Nitric Oxide
  • Prostacyclin
  • Ectonucleotidase CD39

*Defense against Thrombus Formation
VESSEL WALL

• Subendothelial Matrix:
  • Collagen
• Medial (Smooth Muscle) & Adventitial Layers
  • Tissue Factor
  ✦ Disruption of Endothelial Layer:
    ▪ Exposure to Circulating blood
    ▪ Initiates process of Clot Formation
    ▪ Exposure of Collagen causes accumulation and activation of platelets
    ▪ Exposure of Tissue Factor ➔ thrombin:
      ◆ Converts Fibrinogen to Fibrin
      ◆ Activates Platelets
PLATELET ACTIVATION

Underlying Collagen exposed to platelets which bind with Collagen-Specific Glycoprotein Ia/IIa Surface Receptors

This is strengthened by von Willebrand Factor (vWF): released from endothelium and platelets. vWF will also cause additional links with Glycoproteins Ib, IX, V.

Platelet Adherence at the site of Injury

Activated Platelets release granules into plasma (ADP, Serotonin, Platelet-Activating Factor, vWF, Platelet Factor 4 and Thromboxane A2) which in turn activate more platelets.
COAGULATION CASCADE

- Has 2 Pathways which produce Fibrin
  - Intrinsic (Contact Activation)
  - Extrinsic (Tissue Factor)
  - FINAL: COMMON PATHWAY

- Previously: 2 Pathways of equal importance joined to a common pathway

- Now: Primary pathway for thrombogenesis is Tissue Factor Pathway

- Pathways are a series of reactions whereby inactive enzyme precursors are activated by a co-enzyme
TISSUE FACTOR (EXTRINSIC)

- Role: To generate a “Thrombin Burst”

1. Damage to vessel Wall
2. FVII (stable factor) leaves the circulation and makes contact with Tissue Factor (TF) forming TF-FVIIa complex
3. TF-FVIIa activates FIX & FX
4. FXa and co-factor FVa form a prothrombinase complex which activates prothrombin to thrombin
5. Thrombin then activates other components (FV and FVIII) leading to activation FX (tenase complex)
CONTACT ACTIVATION (INTRINSIC)

1. Formation of Primary Complex on Collagen by (HMW Kininogen, Prekallikrein, and FXII (Hageman Factor)
2. Prekallikrein → Kallikrein and FXII → FXIIa
3. FXIIa activates FXI
4. FXIa activates factor IX
5. FIX and FVIIa (tenase complex) which activates FX
FINAL COMMON PATHWAY

• THE DIVISION IS ARTIFICIAL
• FXa converting prothrombin to thrombin
• Thrombin converting fibrinogen to fibrin
• Ultimately leading to the formation of a stable fibrin clot
Intrinsic

- surface contact

- XII \rightarrow XII_a

- XI \rightarrow XI_a

- IX \rightarrow IX_a

- (VIII, PL, Ca^{++})

Common

- prothrombin

- (V, PL, Ca^{++})

- thrombin (serine protease)

- fibrinogen

- (X, PL, Ca^{++})

- fibrin

- XIII

Extrinsic

- TF:VII_a

- tissue damage

- XII – Hageman factor, a serine protease

- XI – Plasma thromboplastin, antecedent serine protease

- IX – Christmas factor, serine protease

- VII – Stable factor, serine protease

- XIII – Fibrin stabilising factor, a transglutaminase

- PL – Platelet membrane phospholipid

- Ca^{++} – Calcium ions

- TF – Tissue Factor (a = active form)

- XIII_a – stable fibrin clot
CO-FACTORS

- Calcium and Phospholipid: required for formation of tenase and Prothrombinase complexes
- Vitamin K: NB for maturation of factors II, VII, IX, X as well as Protein S, C and Z
- Vitamin-K Epoxide Reductase (VKORC): NB reduces Vitamin K to its active form
REGULATORS

5 Mechanisms keep Platelet Activation and Coagulation Cascade in Check

- **Protein C**: Major (Vit K dependant)
  - Physiological Anti Coagulant
- **Anti thrombin**: Degrades: Thrombin, FIXa, FXa, FXIa and FXIIa (def causes thrombophilia)
- **Tissue Factor Pathway Inhibitor**: limits the action of Tissue Factor
- **Plasmin**: Breaks down Fibrin and inhibit excess fibrin production
- **Prostacyclin**: Ultimately causes inhibition of cytoplasmic release by the granules therefore inhibits increased platelet activation
REFERENCES


• Lange’s Physiology