Coagulation Cascade and Hemostasis

Hemostasis is the physiological process that stops bleeding after vascular injury by forming a stable blood clot to seal damaged vessels.

Phases of Hemostasis

1. **Vascular Spasm (Vasoconstriction)**
   Immediate reflex contraction of the damaged blood vessel to reduce blood flow and loss.
   - Endothelial injury exposes collagen fibers, triggering platelet adhesion.
   - Activated platelets release **serotonin (5-HT)** , a potent vasoconstrictor, and **ADP** .
   - Vasoconstriction lasts minutes and is the initial mechanism to limit bleeding.
2. **Platelet Plug Formation (Primary Hemostasis)**
   Platelets adhere to exposed collagen via **von Willebrand factor (vWF)** and become activated.
   Activated platelets:
   - Swell, develop pseudopods, become sticky.
   - Release granules containing ADP, thromboxane A2, which recruit and activate more platelets.
   - Aggregate to form a temporary platelet plug sealing small vascular breaches.
3. **Coagulation (Secondary Hemostasis)**
   Conversion of soluble **fibrinogen** into insoluble **fibrin** , stabilizing the platelet plug.
   - Catalyzed by **thrombin** , formed from **prothrombin** by activated factor X (Xa) in the presence of co-factors.
   - Results in a stable fibrin mesh reinforcing the clot.

The Coagulation Cascade

The cascade consists of three interconnected pathways:

1. Intrinsic Pathway

Activated by contact with exposed collagen (inside the vessel).

- Factor XII ? XIIa activates ? XI ? XIa activates ? IX ? IXa forms a complex with factor VIIIa (activated from VIII released from vWF) ? activates factor X.
- Requires calcium ions (Ca^{2}?) and phospholipids from activated platelets for activation.

2. Extrinsic Pathway

Triggered by tissue injury releasing **tissue factor (thromboplastin, factor III)** from damaged cells.

- Tissue factor activates factor VII ? VIIa activates factor X in presence of Ca^{2}? and

phospholipids.
- Regulated by **tissue factor pathway inhibitor (TFPI)** which inhibits factor Xa and VIIa complex.

3. Common Pathway

- Activated factor X (Xa) forms **prothrombin activator complex** with factor V, Ca²?, and platelet phospholipids.
- Converts prothrombin (II) into thrombin (IIa).
- Thrombin cleaves fibrinogen into fibrin monomers, which polymerize and are cross-linked by factor XIIIa to form a stable clot.

Clot Retraction and Serum Formation

- Platelet pseudopods contract, pulling fibrin mesh together, shrinking clot size by ~40%.
- Edges of the injured vessel are pulled together to facilitate healing.
- Serum (plasma without fibrinogen and clotting factors) is expelled from the clot.

Regulation of Coagulation

Role of Vitamin K

Essential for post-translational modification of clotting factors II (prothrombin), VII, IX, X, and anticoagulant proteins C and S.

- Deficiency leads to bleeding disorders.
- Produced by intestinal bacteria and obtained from green leafy vegetables.

Anticoagulant Mechanisms

Prevent excessive clot formation and maintain blood fluidity:

- **Antithrombin III:** Inactivates factors IXa, Xa, XIa, XIIa; activity enhanced by heparin.
- **Protein C and Protein S:** Activated by thrombin-thrombomodulin complex; degrade factors Va and VIIIa.
- **Prostacyclin (PGI?) and Nitric Oxide (NO):** Released from endothelium, inhibit platelet adhesion and aggregation.
- **Heparin:** Secreted by mast cells and basophils; enhances antithrombin III activity.

Fibrinolysis: Clot Dissolution

- **Plasminogen** is converted to **plasmin** by tissue plasminogen activator (tPA) and urokinase.
- Plasmin degrades fibrin into soluble fragments, dissolving the clot.
- Controlled to prevent excessive clot breakdown.

Clinical pearls

Anticoagulant Drugs

- **Heparin:** Enhances antithrombin III, used in acute thrombotic events.
- **Warfarin:** Vitamin K antagonist, reduces synthesis of vitamin K-dependent clotting factors.
- **tPA and Streptokinase:** Promote fibrinolysis, used in acute myocardial infarction and stroke.

Disorders of Hemostasis

- **Bleeding Disorders:** Due to deficiency of clotting factors (e.g., hemophilia A [factor VIII deficiency], hemophilia B [factor IX deficiency]), vitamin K deficiency, or platelet dysfunction.
- **Excessive Clotting (Thrombosis):** Formation of clots within intact vessels, can lead to embolism and ischemic events (stroke, MI). Risk factors include stasis, endothelial injury, hypercoagulability (Virchow's triad).

Key Clotting Factors

Factor Number	Name	Function	Vitamin K Dependent?
I	Fibrinogen	Precursor to fibrin	No
II	Prothrombin	Precursor to thrombin	Yes
III	Tissue Factor	Initiates extrinsic pathway	No
IV	Calcium	Required cofactor	No
V	Labile Factor	Cofactor in prothrombin activator	No
VII	Stable Factor	Extrinsic pathway initiator	Yes
VIII	Anti-hemophilic A	Cofactor intrinsic pathway	No
IX	Anti-hemophilic B	Intrinsic pathway	Yes
X	Stuart-Prower	Common pathway	Yes
XI	Plasma thromboplastin antecedent	Intrinsic pathway	No
XII	Hageman factor	Intrinsic pathway	No
XIII	Fibrin-stabilizing factor	Crosslinks fibrin mesh	No