Clotting factors and Coagulation

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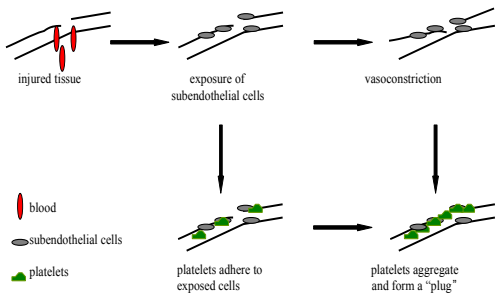
Hemostasis

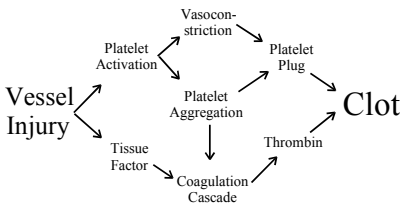
- Hemostasis is defined as a property of circulation whereby blood is maintained within a vessel and the ability of the system to prevent excessive blood loss when injured.
- One of the major components needed to provide hemostasis is the coagulation system which involves the clotting proteins or **clotting factors.**
- The coagulation factors, except for calcium and thromboplastin, are proteins and are involved in a sequential reaction or coagulation cascade.
- The last step of the cascade leads to insoluble fibrin as the end product.
- The reactions leading to fibrin formation can be divided into the **extrinsic, intrinsic and common pathways.**

NORMAL COAGULATION

- There are **3 stages** in normal coagulation: primary hemostasis, secondary hemostasis and tertiary hemostasis.
- Primary hemostasis is provided by platelets.
- Secondary hemostasis is provided by the plasma protein clotting factors, ie, fibrin clot formation.
- Tertiary hemostasis is the formation of fibrin polymers and their subsequent resolution through fibrinolysis.



Overview of blood coagulation



The "Cascade" Theory

- Blood coagulation is a series of biochemical reactions.
- Transforms circulating substances into insoluble gel.
- Converts soluble fibrinogen into fibrin.
- Process requires plasma proteins, phospholipids and calcium.

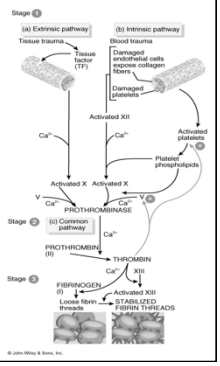
Factor Number	Common Name
I	Fibrinogen
II	Prothrombin
III	Tissue Factor
IV	Ca2+
Va	Proaccelerin
VII	Proconvertin
VIII	Antihemophilic Factor
IX	Christmas Factor
X	Stuart Factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin Stabilizing Factor

The Blood Clotting Cascade

- **Extrinsic Pathway (Fast acting)**

  1. Tissue Factor (TF) or Thromboplastin is released by tissue cells outside of the damaged vessel.

  2. TF begins a chemical reaction pathway that activates Thrombokinase (F10). F10 combines with Proaccelerin (F5) to form the enzyme Prothrombinase.



The Blood Clotting Cascade

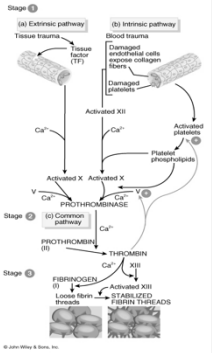
- **Intrinsic Pathway (slow acting)**

  Activated by factors within the blood or vessels

  Antihemophilic factor D or Hageman factor (F12) is activated by contact with collagen fibers.

  F12 starts a chemical cascade that ultimately activates F10 or Thrombokinase.

  F10 combines with Proaccelerin (F5) to form the enzyme Prothrombinase.



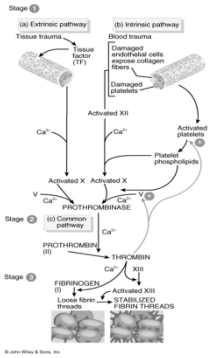
The Blood Clotting Cascade

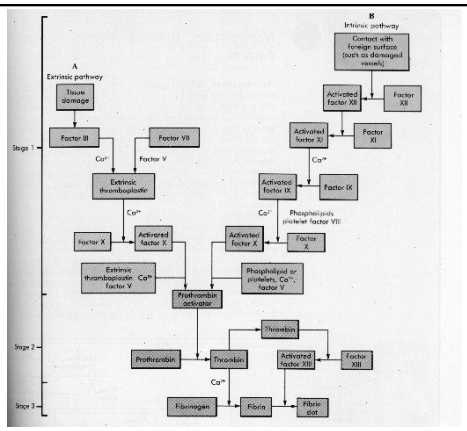
- **The Common Pathway**

  Prothrombinase catalyzes the conversion of Prothrombin (F2) to Thrombin.

  Thrombin converts the soluble plasma protein fibrinogen in the insoluble protein fibrin (loose threads).

  Thrombin also activates Fibrin Stabilizing Factor (F13) which converts the loose threads into stable threads.



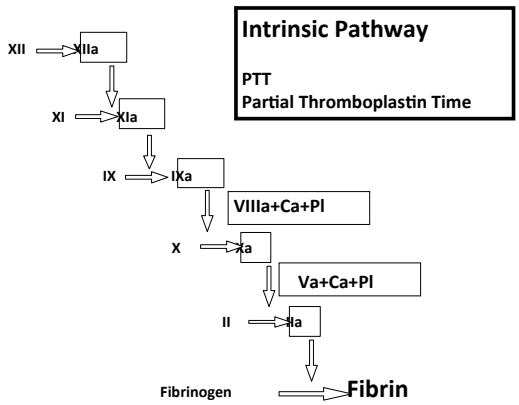


Overview

- A fibrin clot is the end product of coagulation.
- Clotting via the tissue factor pathway (extrinsic) starts when blood is in contact with tissue factor (TF).
- The intrinsic pathway (a relatively slow process) begins with exposure of a foreign surface like collagen as a result of endothelium damage.
- Factors unique to the intrinsic pathway are XII, prekallikrein, HK, XI, IX and cofactor VIII.
- The tissue factor pathway includes TF and VII.
- Both pathways lead to the common pathway which consists of factor X, cofactor V, Pf3, Ca++, prothrombin and fibrinogen.
- The final product of coagulation is cross-linked fibrin, produced in response to factor XIII, Ca++ and thrombin.

Intrinsic Pathway (*Contact Activation pathway*)

- All procoagulants circulate as inactive precursors.
- Activated in vivo by endothelial injury, in vitro by glass or other contact
- A foreign surface such as collagen activates factor XII.
- Acting as catalysts are HK and kallikrein in the contact phase.
- Calcium is involved in three steps: the activation of IX, X and prothrombin.
- Cofactor VIII interacts in the activation of factor X and cofactor V reacts with prothrombin.
- The platelet phospholipid surface acts as template in the activation of X and prothrombin.



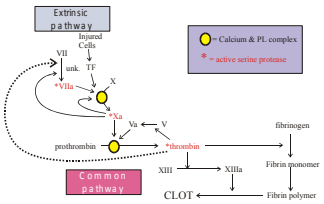
Extrinsic Pathway (*Tissue Factor pathway*)

- The extrinsic pathway is initiated by the release of tissue thromboplastin **(Factor III)** which is exposed to the blood when there is damage to the blood vessel.
- **Factor VII** which is a circulation coagulation factor, forms a complex with tissue thromboplastin and calcium.
- This complex rapidly converts **Factor X** to the enzyme form **Factor Xa.**
- **Factor Xa** catalyzes the prothrombin **(Factor II)** to thrombin **(Factor IIa)** reaction which is needed to convert fibrinogen **(Factor I)** to fibrin.

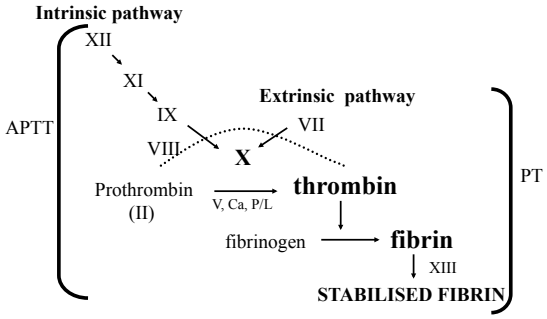
Extrinsic Pathway

- Cell injury activates tissue thromboplastin (Factor III)
- III complexes with Ca++ and VII to activate X
- Xa complexes with V, PF3 and Ca++ to form active tissue thromboplastin
- II Prothrombin tissue thromboplastin → thrombin IIa
- I Fibrinogen thrombin IIa → fibrin Ia
- Factor XIII activated by Ca++ and thrombin IIa
- XIIIa and Ca++ stabilize fibrin clot

Extrinsic Pathway



Coagulation cascade



Coagulation Cascade

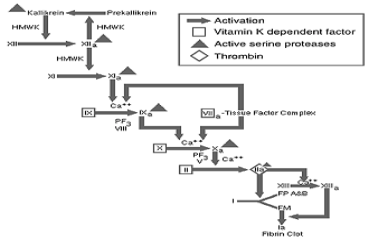


Figure 3. The coagulation cascade, including both intrinsic and extrinsic pathways.

Extrinsic Pathway

- The **Prothrombin Time** or **PT** is a laboratory screening test used to detect coagulation disorders.
- It measures the activity of the factors of the extrinsic pathway including factors **II, V, VII, X,** and **I (fibrinogen).**
- The extrinsic factors not measured in the **PT** test are **Factors III (Thromboplastin)**, and **IV (Calcium)**.
- The **PT** is also used to monitor oral anticoagulant therapy such as **warfarin**.

Fibrinolysis

- The last stage of coagulation is **fibrinolysis,** which is the dissolution and localization of a fibrin clot.
- Prevents excessive fibrin deposition
- Allows closely coupled with fibrin formation
- Localized surface bound phenomenon that is catalyzed by fibrin formation

Fibrinolysis

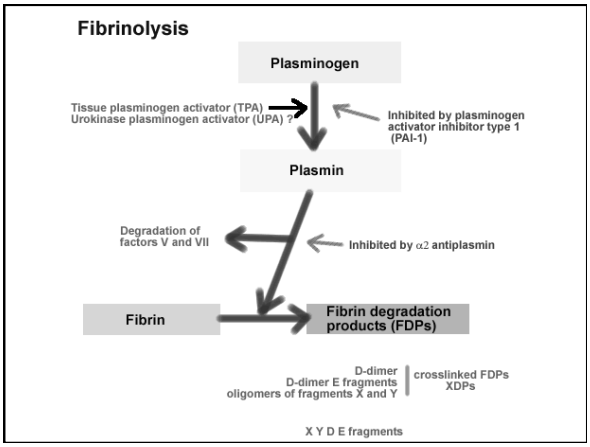
- Fibrinolytic system is a complement to the coagulation system – a fine balance between the two systems must occur
  - Restricts fibrin formation to area of injury
  - Dissolves clot by digestion of fibrin
- Initiated when coagulation begins – will ultimately dissolve clot
- plasminogen
  ↓
- Fibrin plasmin → fibrin degradation products (FDPs)

Components: fibrinolysis

- Plasminogen -> plasmin
- Plasminogen activators
- Inactivators of plasminogen
- Inhibitors of plasmin

Fibrinolysis

- Plasminogen is activated and converts to plasmin by factor XII, HMWK,and PK
- **Plasmin** = enzyme which dissolves fibrin clots into protein fragments that are cleared from plasma by the liver
- Fibrin degradation products are breakdown fragments of fibrin or fibrinogen.
  - The protein fragments are designated X, Y, D, and E
  - Fragments are strong inhibitors of further coagulation by
    - interfering with the action of thrombin
    - interfering with platelet aggregation



Fibrinolysis

- Inhibitors of fibrinolysis = antiplasmins.
- Used to regulate and limit plasmin activity and fibrinolysis
  - alpha-2-antiplasmin
  - alpha-2-macroglobulin

Fibrinolysis

- Many conditions can affect the fibrinolytic system resulting in an increased or decreased activity of fibrinolysis.
- Examples of such conditions are Disseminated Intravascular Coagulation **(DIC)**, trauma from surgical procedures or accidents, deficiencies in or consumption of the various inhibitors and activators of the fibrinolytic system.

Coagulation Inhibitors

- Once Coagulation is initiated, the body has mechanisms for avoiding massive thrombus formation.
- Physiologic balancing of the Hemostatic mechanism to limit uncontrolled bleeding and clotting is an important aspect in the Hemostatic response.
- There are a variety of biological control mechanisms which aid in the control of blood coagulation.
- These include the ability of the liver and the reticulo-endothelial system to clear activated clotting factors from the circulation, the prevention of the high concentrations of activated factors at a given location within the circulation by a constant blood flow, and natural inhibitors in the plasma such as **Antithrombin III** and the **Protein C-S System**

Antithrombin III (AT-III)

- Most important since it can also inhibit the activities of factors IXa, Xa, XIa and XIIa.
- **AT-III** binds to activated factors rendering them inactive
- The primary functin is to inactivate Thrombin, attaches to Thrombin IIa and inactivates it, preventing thrombin from converting fibrinogen to fibrin
- The action of AT-III is enhanced and accelerated by the presence of Heparin (either naturally released from basophils or given therapeutically as an anticoagulant)
- AT-III also inactivates other factors: XII, XI, X, IX and Kallekrein
- Patients with decreased **AT-III** levels are subject to an increased risk of thromboembolism even in cases of slightly reduced **AT-III** levels.

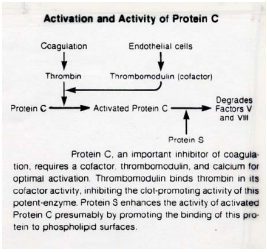
Protein S

- Produced by liver
- Vitamin K dependent
- Acts as a cofactor to Protein C to enhance its ability to degrade factors V and VIII

Protein C

- Produced by liver
- Vitamin K dependent
- Inactivates factors V and VIII:C
- Protein C is activated by Thrombin (IIa)
- Enhancement of **Protein C** anticoagulant functions is achieved by **Protein S**.
- Patients with **Protein C** and/or **Protein S** deficiencies have a thrombotic tendency.
- Patients also may acquire deficiencies of **Protein C** and **Protein S** with liver disease and disseminated intravascular coagulation **(DIC)**.

Protein C and Protein S



Therapeutic Anticoagulants

- **Heparin**
- **Coumadin (Warfarin, Dicoumarol)**
- **Aspirin**

Heparin

- Administered IV
- Causes immediate inhibition of blood clotting
- Accelerates the action of ATIII to inactivate Thrombin IIa
- Monitored using the PTT test

Coumadin (Warfarin, Dicoumarol)

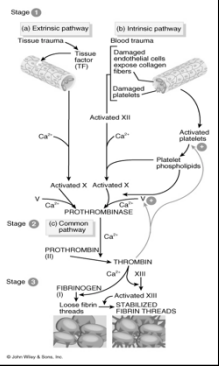
- Oral anticoagulant
- Takes couple days for effects to show
- Inhibits production of vitamin K dependent factors (II, VII, IX, X) (Protein C & S)
- Monitored using the PT test (since factor VII has the shortest ½ life and becomes deficient first)

Aspirin

- Administration results in irreversible inhibition of the platelet enzyme cyclooxygenase, which is needed for proper platelet aggregation (plt adhesion is unaffected)
- Affects last for the lifetime of the platelets – at least seven days
- Patients undergoing certain platelet function tests should avoid aspirin ingestion for at least seven days

The Problems with Clotting Cascade

- **Hemophilia A:** Deficiency of Factor VIII accounts for 85% cases.
  - Almost exclusively in males. Females are usually carriers
  - caused by a gene mutation on the "X" chromosome. Occurs in about 1/10,000 male births
- **Other Hemophilias** account for another 15%
  - **Hemophilia B** (Factor IX)
  - **Hemophilia C** (Factor XI)
  - **Hemophilia D** (Factor XII)



The Problems with Platelets and Abnormal Clotting

- **Thrombocytopenia:** Abnormally low levels of platelets. Usually below 50,000/ul of blood.
  - In many cases, specific antibodies are produced against platelets destroying them
- **Thrombus:** Abnormal clot that develops in a blood vessel.
- **Embolus:** Free thrombic clots carried the blood that usually get caught in arterioles in the brain, kidney, and lungs.