بسم الله الرحمن الرحيم

Physiology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

FINAL | Lecture 3

Hemostasis & Blood Coagulation (Pt. 2)

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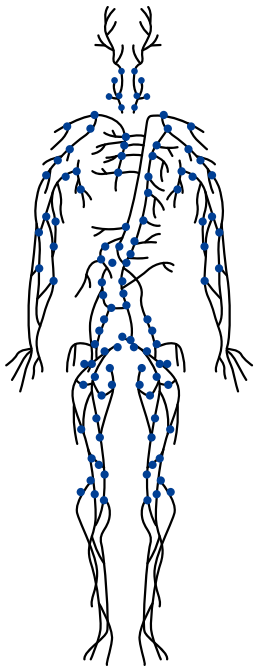


Generating Prothrombin Activator

- Two pathways:
  - Extrinsic pathway – Trauma to **vessel wall** and adjacent tissues
  - Intrinsic pathway – Trauma to the **blood** or **exposure of the blood to collagen**
- Both pathways involve "**clotting factors**"— mostly inactive **proteases** that are activated in **cascades**

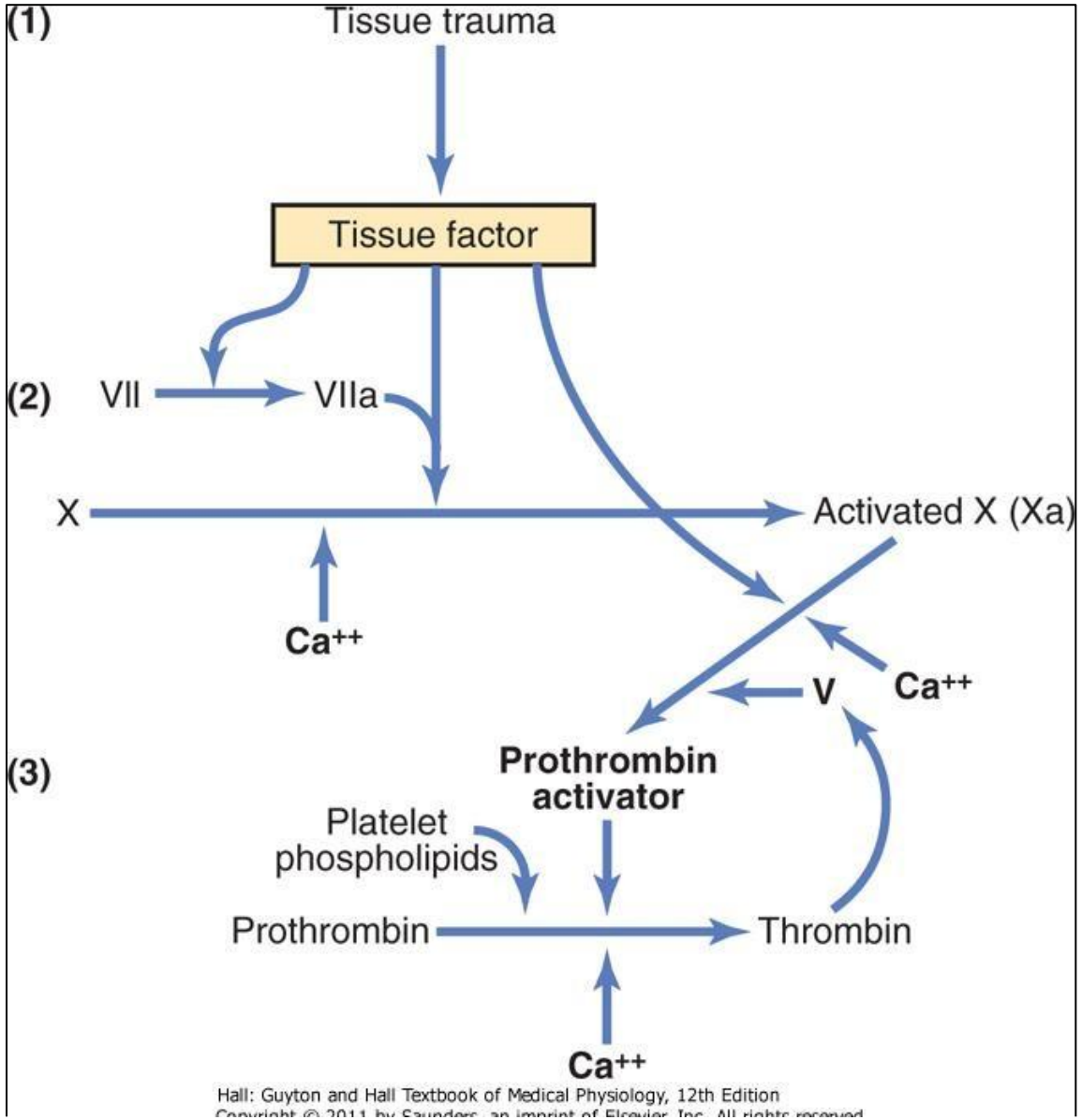
Generating Prothrombin Activator

- The coagulation process involves two main pathways that lead to the formation of the **prothrombinase complex (also called the prothrombin activator complex)**, which converts prothrombin into thrombin.

1. **Extrinsic pathway:**
   - This pathway is **triggered by damage to the vessel wall or surrounding tissues**. The injured tissue **releases tissue factor (TF, also known as Factor III or Thromboplastin)** at the site of injury.
2. **Intrinsic pathway:**
   - This pathway begins when there is **damage within the blood vessels** or when **collagen becomes exposed to circulating blood components**.
   - For example, when blood contacts a **rough surface (such as a glass tube)**, the **intrinsic pathway is activated**.

- Most clotting factors circulate in the blood as **inactive zymogens (precursors of proteases)**, which are **sequentially activated in a cascade reaction.**

Extrinsic Pathway of Blood Clotting



Blood Coagulation — **Extrinsic Pathway**

- Release of tissue factor
- Activation of Factor X- role of Factor VII and tissue factor
- Effect of Xa to form prothrombin activator -role of Factor V in the presence of calcium and phospholipids to split prothrombin to thrombin
- **Thrombin Positive Feedback**
  - Thrombin not only converts **fibrinogen into fibrin but** also **enhances its own production** through a **positive feedback mechanism**.
  - It **activates Factor V, which accelerates the generation of additional thrombin.**

Extrinsic Pathway of Blood Clotting

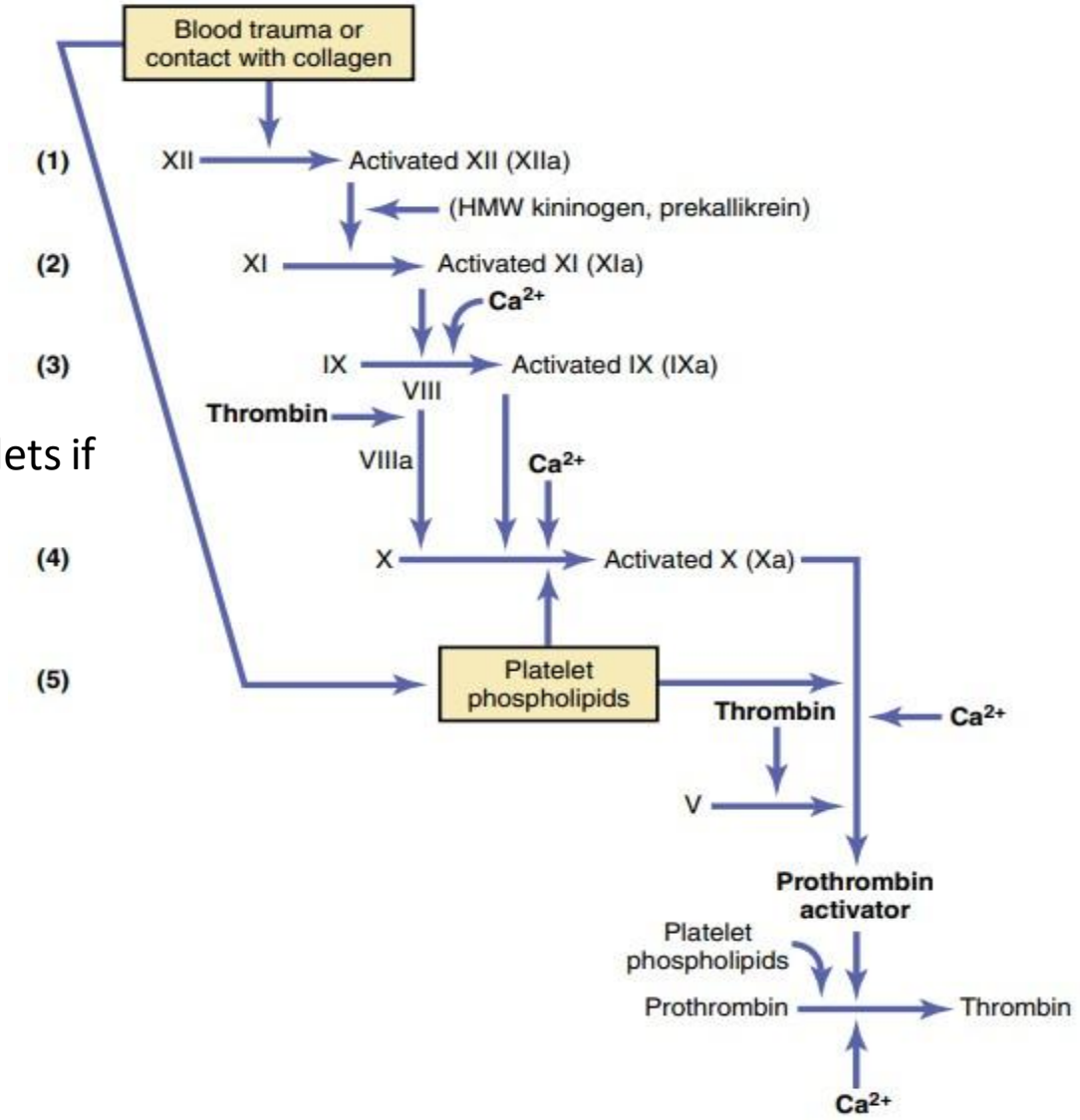
- The extrinsic pathway is initiated by **tissue trauma that exposes tissue factor (Factor III)** to the blood.
- **Tissue factor is a lipoprotein complex with enzymatic activity associated with phospholipids.** Do your own research.
- Tissue factor **binds to** Factor VII (inactive form).
- This interaction **converts** Factor VII into **Factor VIIa**.
- The **TF–VIIa complex then activates Factor X** in the presence of calcium ions (Ca^{2+}).

Extrinsic Pathway of Blood Clotting

- Activated Factor X (Xa) plays a central role in forming the **prothrombinase complex**, which consists of:
  - **Factor Xa** (the active protease)
  - **Factor V**
  - **Calcium ions (Ca^{2+})**
  - **Phospholipids from cell membranes or platelets**
- This complex converts **prothrombin (Factor II)** into **thrombin (Factor IIa)**.
- **Platelet phospholipids provide a surface that accelerates the reaction.**
- **Factor V**, initially inactive, is **activated by thrombin**, which greatly **enhances the activity of the prothrombinase complex—up to several thousand-fold.**
- Thus, **Factor Xa** is the main protease in this complex, and **Ca^{2+} is essential** for the entire reaction.

Intrinsic Pathway of Blood Clotting

VIII or platelets if def, 4 is def



Blood Coagulation — **Intrinsic Pathway**

- Blood trauma causes activation Factor XII and release of platelet phospholipids
- Activation of Factor XI
- Activation of Factor IX by activated XI
- Activation of Factor X-role of Factor VIII
- Action of activated Factor X to form prothrombin activator-role of Factor V
- Thrombin **amplifies its own generation** through **positive feedback mechanisms** by:
  - **Activating Factor VIII**, which **enhances the activation of Factor X** through the **tenase complex.**
  - **Activating Factor V**, which **strengthens the prothrombinase complex** and **accelerates thrombin formation.**
- These **feedback loops ensure rapid and localized clot formation** at the site of injury.

Intrinsic Pathway of Blood Clotting

- The **intrinsic pathway** is initiated by:
  - **Trauma to blood components**, or
  - **Exposure of collagen** in a damaged vessel wall.
- This triggers a **cascade of reactions:**
  - **Activation of Factor XII (Hageman factor):**
    - When blood contacts **collagen or a negatively charged surface**, Factor XII **undergoes a conformational change** and becomes **activated (XIIa).**
  - **Platelet activation:**
    - Damaged platelets expose **negatively charged phospholipids (previously called platelet factor 3, PF3)**, which **provide a catalytic surface** for the cascade reactions.
  - **Activation of Factor XI:**
    - Factor XIIa, with the help of **high-molecular-weight kininogen (HMWK)** and **prekallikrein, activates Factor XI.**

Intrinsic Pathway of Blood Clotting

- **Activation of Factor IX:**
  - Activated Factor XI (**XIa**), in the presence of **calcium ions (Ca^{2+})**, **activates Factor IX**.
- **Formation of the tenase complex:**
  - Activated Factor IX (**IXa**) combines with **Factor VIIIa** (which is **activated by thrombin**), **Ca^{2+}**, and **platelet phospholipids (PF3)** to form the **tenase complex**, which **activates Factor X**.
- **Formation of prothrombinase:**
  - Once **Factor X is activated (Xa)**, it forms the **prothrombinase complex** together with **Factor V**, **Ca^{2+}**, and **platelet phospholipids, as in the extrinsic pathway.**
- **Thrombin further activates Factors V and VIII**, greatly **amplifying clot formation.**
- A **deficiency in Factor VIII or platelet phospholipids** can **impair Factor X activation**, thereby **slowing or preventing coagulation.**

Synergy between the Intrinsic and Extrinsic Pathways

- Both pathways can act together **synergistically**, as they **converge at a common point**, which is the assembly of **the prothrombinase (prothrombin activator) complex**.
- Tissue injury…
  - Tissue factor activates the **Extrinsic Pathway**
  - Exposure of Factor XII and platelets to collagen activates the **Intrinsic Pathway**
- Extrinsic pathway can be **explosive**, with clotting in <15 seconds, since it has less steps. However, it is limited in terms of TF, X, VII, V amounts.
- The Intrinsic pathway is slower → 1 – 6 minutes would be need to form a clot if this pathway is activated alone.

Prevention of Clotting

- **Anti-coagulation is also crucial and there are many mechanisms for clot prevention, such as:**
- Smoothness of the endothelial surface
- Mucopolysaccharide coating (glycocalyx) repels platelets and clotting factors
- Thrombomodulin, bound to the endothelial surface, binds thrombin, **localizing** it and **altering its substrate specificity**, thereby causing thrombin to lose its ability to convert fibrinogen into fibrin.
- Also, the **Thrombin-thrombomodulin complex** activates **Protein C** → inactivates **factors V and VIII**
- Damage to glycocalyx activates factor XII & platelets (intrinsic pathway).
- If collagen is exposed → even more robust activation of the intrinsic pathway.

Negative Feedback

- Regulates the explosive nature of thrombin activation done by positive feedback
- **Fibrin fibers** bind 85-90% of thrombin and localize it to the clot
- **Antithrombin III** combines with the remainder and inactivates it over 12-20 minutes

Heparin

- It is an important anticoagulant found in our body, but physiologically, its availability is limited.
- Used therapeutically
- Highly negatively charged
- Binds anti-thrombin III and increases its effectiveness 100- to 1000-fold
- Heparin-antithrombin III removes free thrombin from the blood almost instantly
- Also removes XIIa, XIa, Xa, and IXa
- Produced by **mast cells**, **basophils** and it is particularly abundant in **pericapillary regions of liver and lung** because these areas have slow blood flow and are prone to clot formation.
- **Thus, heparin plays an essential role in preventing local coagulation in these regions.**

Clot Lysis

- At first Plasminogen is trapped in the clot with platelets and other factors, and its amount is low.
- Over several days, injured tissues release tissue plasminogen activator (tPA)
- Plasminogen is activated to plasmin, a protease resembling **trypsin**.
- Plasmin digests fibrin fibers and several other clotting factors, thereby removing and digesting the clot.
- Often results in re-opening repaired small blood vessels, a phenomenon known as recanalization.

PHYSIOLOGY QUIZ

LECTURE 10

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			