

# Physiology of Hemostasis and Coagulation Cascade

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**Coagulation is a dynamic process. The concept of blood coagulation started to emerge in the medical literature in 1960. In that year, Davie, Ratnoff, and Macfarlane published an article that described for the first time a cascade of events that outline the coagulation process. Hemostasis can be defined as the arrest of bleeding. The term derives from two Greek words that mean blood and stop. The process of hemostasis is maintained by complicated interactions between the coagulation and anticoagulation systems in addition to the platelets and blood vessel wall.**



## A Summary of the Thrombogenic and Antithrombogenic Components Involved in Hemostasis

The process of hemostasis includes a tight **balance between thrombogenic and anti-thrombogenic components** which are found normally or pathologically in our bodies. The following table summarizes the most common thrombogenic and anti-thrombogenic

components involved mainly in the initiation of the process of hemostasis.

<b>Thrombogenic Components</b>	<b>Antithrombogenic Components</b>
Exposed endothelium in an injured blood vessel	Heparin
Tissue factor	Thrombomodulin
Exposure of collagen	Tissue plasminogen activator
Platelets	Antithrombin
Platelet-activating factor	Protein C and S
Clotting factors	Plasminogen
Prothrombin	
Fibrinogen	
Von Willebrand factor	

## Primary Hemostasis

Primary hemostasis refers to the first phase of the hemostasis process that stops bleeding. It is a result of the interaction between the circulating platelets, the blood vessel wall, and adhesive proteins leading to the **formation of the initial platelet plug**. The process is preceded by vasoconstriction and followed by secondary hemostasis.

The normal lining of a blood vessel known as the endothelium is an anti-thrombogenic component. Therefore, in physiologic conditions, a platelet plug should not form in an otherwise healthy blood vessel without any endothelial injury.

The subendothelial layer is highly thrombogenic because it contains collagen, tissue factor, [Von Willebrand factor](#), and laminin. Therefore, an injured blood vessel with exposed endothelium and the subendothelial layer is a potent initiator of the coagulation cascade.

The platelets do not adhere to intact vascular endothelium. They, however, strongly adhere to collagen and von Willebrand factor, both are abundantly available in the subendothelial layer. The process of primary hemostasis occurs in three main steps:

### 1. Platelet Adhesion

If the blood vessel wall gets injured, the von Willebrand factor becomes exposed. This factor acts as a bridge between endothelial collagen and platelet surface receptors known as GpIb. The interaction between von Willebrand factor, collagen, and platelet surface receptor GpIb results in [platelet](#) adhesion.

### 2. Platelet Secretion

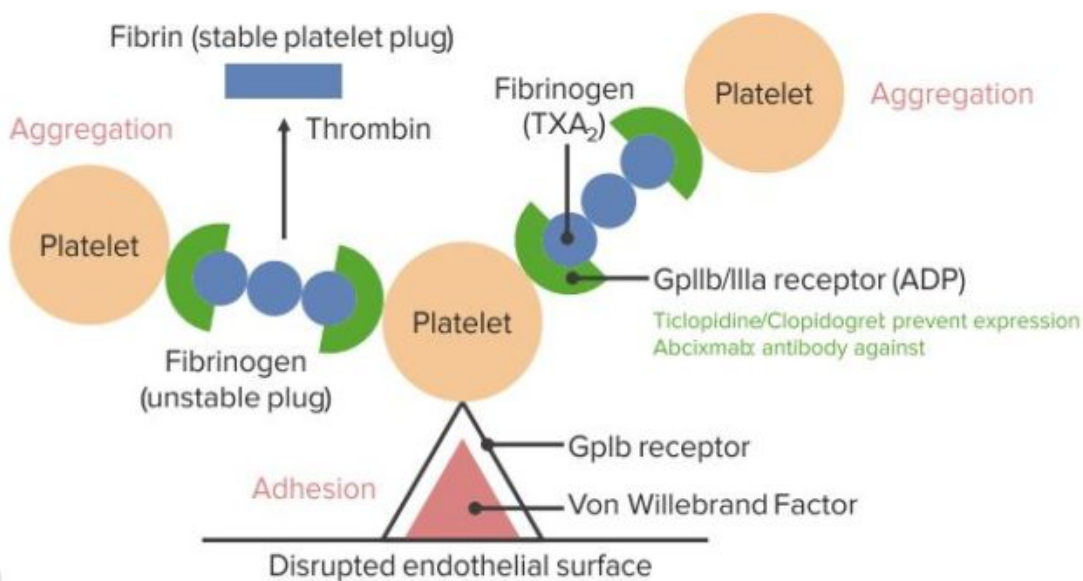
Platelets have **two types of granules that contain many thrombogenic factors**. The first type of granules contains P-selectin, fibrinogen, fibronectin, factor V, factor VIII, factor IV, platelet-derived growth factor, and tumor growth factor-alpha and is known as alpha granules. The second type contains ATP, DP, calcium, serotonin, histamine, and epinephrine and is known as Dense granules.

After platelet adhesion, degranulation from both types of platelet granules takes place. Different factors are released including calcium. The release of calcium in this step is essential for platelet activation and the assembly of other coagulation factors.

### 3. Platelet Aggregation

The activated platelets secrete thromboxane A<sub>2</sub> which stimulates further platelet aggregation. When combined with ADP, thromboxane A<sub>2</sub> leads to enlargement of the initial platelet plug and temporary seal of the vascular injury. Moreover, ADP also binds to the platelet receptor known as GpIIb/IIIa which is responsible for the deposition of fibrinogen. Thrombin generation converts fibrinogen to fibrin which adds more the stability of the initial platelet plug. At this stage, we enter what is known as secondary hemostasis.

Prostacyclin is also released at this stage. This is an anti-thrombogenic factor that limits platelet aggregation to the injured area.



"Temporary Hemostatic Plug" Image created by Lecturio

### Coagulation Cascade

Classically speaking, the coagulation cascade has been **classified into intrinsic and extrinsic pathways**. Both pathways converge on factor X activation.

The extrinsic pathway is the first step in plasma-mediated hemostasis. It is activated by tissue factor which is not normally found in the plasma, i.e. blood vessel wall injury is needed to initiate this pathway. Tissue factor binds to clotting factor VIIa and calcium which promote the conversion of factor X to factor Xa to start the common pathway.

The intrinsic pathway starts with the activation of thrombin by factor XIII. It starts with factor XII, HMW kininogen, prekallikrein, and factor XI which all lead to the activation of factor XI. Activated factor XI activates factor IX. Activated factor IX along with factor VIII form a tenase complex on a phospholipid surface which is responsible for the activation of factor X. After that, the common coagulation pathway is started.

Activation factor X along with cofactor factor V, tissue phospholipids, platelet phospholipids, and calcium forms prothrombinase complex which converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin and activates factor XIII which cross-links fibrin polymers to stabilize the initial platelet plug. By this process, we have formed a definitive secondary hemostatic plug.

The following points summarize the three pathways involved in coagulation according to this early classical concept:

<b>Intrinsic pathway</b>	XII à XI à IX à VIII à Common pathway
<b>Extrinsic pathway</b>	III and Tissue factor à VII à Common pathway
<b>Common pathway</b>	X à V à II à Formation of a definitive secondary hemostatic plug

## Current Concept of Coagulation

The classical concept of an intrinsic and extrinsic pathway of coagulation can make one think that both systems act independently from each other. Moreover, it can give the impression that there is not a strict quality-control system that governs both pathways. The current concept states that the intrinsic pathway is, in fact, an **augmentation step of the extrinsic pathway**. The current model of our understanding of coagulation cascade can be summarized in the following four steps:

### 1. Initiation of Coagulation Cascade

The expression of tissue factor in a damaged vessel binds factor VIIa to activate factor IX. This complex activates factor X. The activated factor Xa binds to factor II to form thrombin. Thrombin generation in this step is limited. If the tissue factor pathway inhibitor is available, the generation of thrombin can be interrupted at this stage.

### 2. Amplification Step

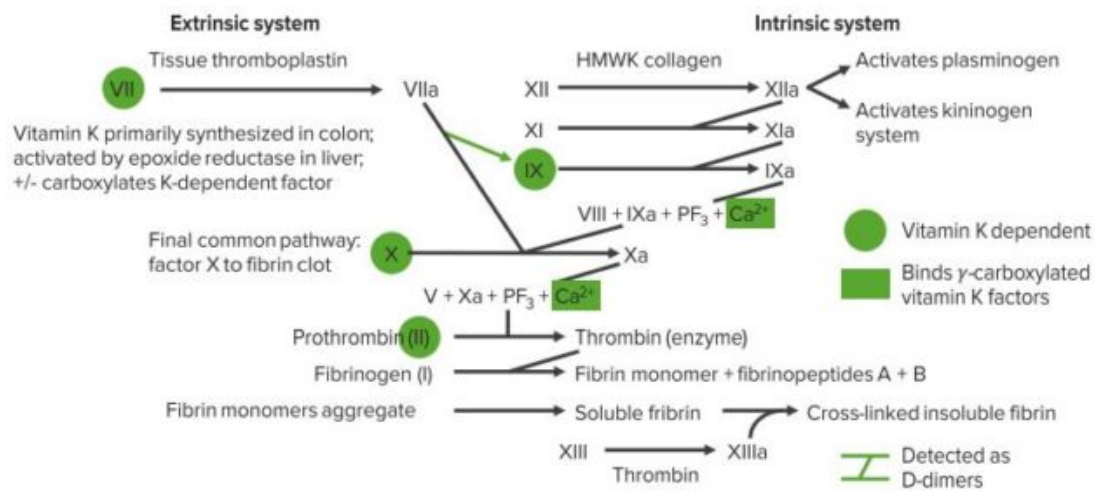
The amount of generated thrombin in the initiation step is not enough to convert substantial amounts of fibrinogen to fibrin. A positive feedback loop develops which bind thrombin with platelets. Thrombin generation in the initiation step activates factors V and VIII. The activation of these two factors accelerates the activation of factor II by factor Xa and factor Xa by factor IXa. This is maintained by the action of a prothrombinase complex.

### 3. Propagation Step

The prothrombinase complex and tenase complex accumulate on the platelet surface. Robust amounts of thrombin are generated, and platelets get activated. Fibrin is generated from fibrinogen in sufficient amounts to form a large clot.

### 4. Stabilization Step

The final step is to stabilize the formed clot. Thrombin activates factor XIII which links fibrin polymers to provide strength and stability to the secondary hemostatic plug. Thrombin also activates thrombin activatable fibrinolysis inhibitor (TAFI) which prevents the fibrinolysis of the newly formed clot.



"Coagulation Cascade" Image created by Lecturio

## References

Palta S, Saroa R, Palta A. Overview of the coagulation system. *Indian Journal of Anaesthesia*. 2014;58(5):515-523. doi:10.4103/0019-5049.144643.

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