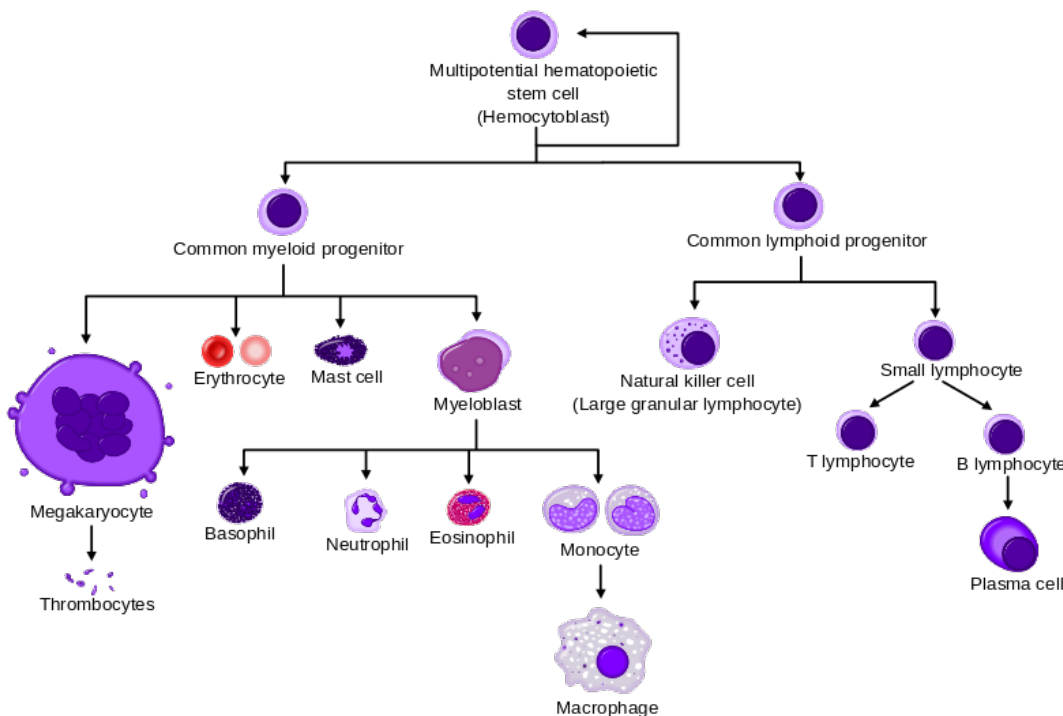


# Biochemistry of Blood

[See online here](#)

In a multicellular organism, most cells cannot migrate to obtain oxygen or to eliminate carbon dioxide. The blood and interstitial fluid fulfill these tasks. The blood consists of roughly 45% solid elements - the blood corpuscles (erythrocytes, leukocytes, and thrombocytes), and approx. 55% solute substances (water, proteins, etc.) - the blood plasma. This article provides an overview of hemoglobin, blood types, and the basics of transfusion medicine as well as a profound insight into hemostasis.



## Structure and Function of Hemoglobin

Red blood cells (RBCs), also called erythrocytes, have a diameter of about 7–8  $\mu\text{m}$ , a simple structure, and – like all other blood corpuscles – originate from **pluripotent bone marrow stem cells**.

The main task of the erythrocytes is oxygen transportation.

Since they do not have a nucleus, they can use all of their inner space for **oxygen transport**. Another reason why erythrocytes are highly specialized is the fact that they do not have mitochondria. Thus, they produce adenosine triphosphate (ATP) anaerobically, i.e. without oxygen. This way, they do not use any of the oxygen it is transporting.

Their special shape as a biconcave disc allows them to have a much larger surface for the

diffusion of gas molecules into and out of the RBCs than, e.g., a sphere would have. Furthermore, their shape is indispensable for the deformation of the erythrocytes when flowing through the narrow capillaries.

Each RBC contains about 280 million hemoglobin molecules.

A **hemoglobin molecule** consists of the following parts:

- A protein part, **globin**, which consists of 4 polypeptide chains.
- Non-protein pigment, the **heme**, which is bound to each of the 4 chains.
- **Iron ion (Fe<sup>2+</sup>)**, which is located in the center of the heme ring and can reversibly bind oxygen.

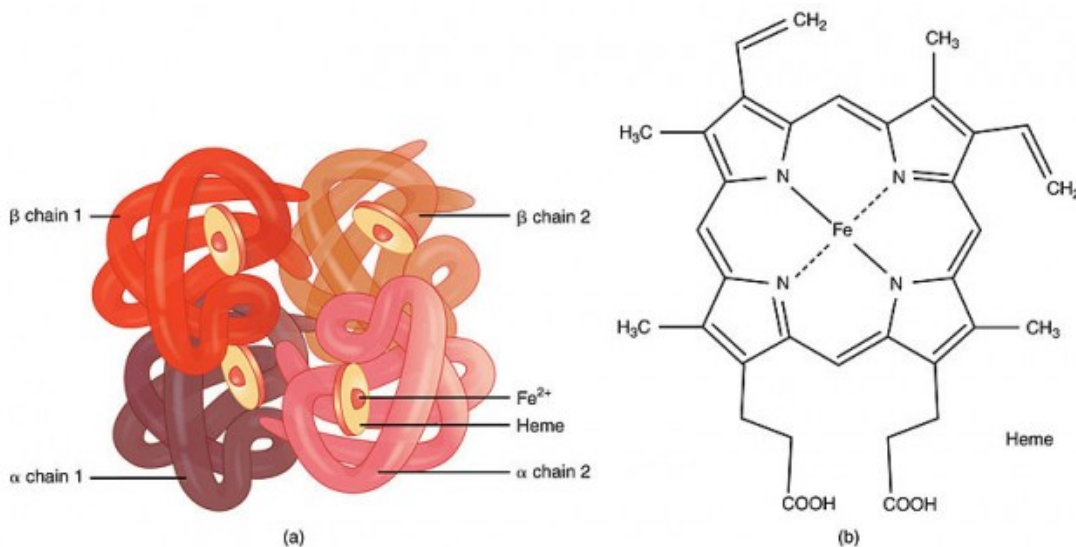


Image: Hemoglobin. By OpenStax College, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Each oxygen molecule incorporated by the lungs is bound to an iron ion. The iron-oxygen reaction reverses while the blood flows through the capillaries. Hereby, the hemoglobin releases oxygen, which diffuses into the interstitial fluid and then into the cells.

The blood in the capillaries absorbs **carbon dioxide**, whereas a part of it binds to hemoglobin amino acids. In the lungs, carbon dioxide is released by the hemoglobin and is exhaled.

Besides the oxygen and carbon dioxide transportation, hemoglobin has another important task - **buffering**. In a similar manner like oxygen and carbon dioxide, hydrogen ions (H<sup>+</sup>) are absorbed and released to reduce changes in the pH of the blood.

Besides the mentioned functions, hemoglobin also plays a role in the regulation of blood flow and blood pressure. The gaseous hormone **nitric oxide** (NO) binds to hemoglobin. When the oxygen tension is decreased, NO is released that leads to **vasodilation** (an increase in diameter of the blood vessel). The consequence is that the blood flow is increased and in the areas, NO is released supplementation with oxygen is improved.

## Life Cycle of Erythrocytes – Heme Biosynthesis, Heme Degradation, and Iron Metabolism

Erythrocytes have a lifespan of about 120 days since their plasma membrane abrades when crossing the narrow blood capillaries. As the RBCs do not have a nucleus or other

organelles, they cannot synthesize new components to replace damaged ones. Stuck or damaged erythrocytes are removed from the circulation and degraded in the spleen and the liver.

In the following steps, the process of the by-products, which are partially reused or excreted, is explained.

## 1. Phagocytosis

In the spleen, the liver, and in the red bone marrow, macrophages phagocytize damaged or deformed erythrocytes.

## 2. Separation

From the hemoglobin, the **globin** and **heme components** are separated.

## 3. Decomposition

Globin is decomposed into individual **amino acids**, which can be reused for the synthesis of other proteins.

## 4. Transferrin

**Iron** is released as  $Fe^{3+}$  from heme and binds to the transporter of  $Fe^{3+}$  in the blood, the transferrin.

## 5. Ferritin

The  $Fe^{3+}$  is decoupled from transferrin, inter alia, in the muscle fibers, the spleen, and the liver and is then bound to the iron storage protein ferritin.

## 6. Release

When absorbed in the gastrointestinal tract or released from the storage,  $Fe^{3+}$  is again coupled with transferrin.

## 7. Bone marrow and hemoglobin synthesis

The  $Fe^{3+}$ -transferrin complex is transported to the red bone marrow and taken in for hemoglobin synthesis. Iron, globin, and vitamin B12 are necessary for hemoglobin synthesis.

## 8. Erythropoietin

With the help of erythropoietin, RBCs are produced in the bone marrow and then enter the blood circulation.

## 9. Elimination of the non-iron part

The non-iron-part of the heme group is primarily converted to biliverdin and later to bilirubin, a yellow-orange pigment.

## 10. Bilirubin

Via the bloodstream, bilirubin is transported into the liver.

## 11. Liver

From the liver cells, bilirubin is given to the bile, which reaches the small and large bowel after being released.

## 12. Colon

With the help of bacteria, bilirubin is converted to **urobilinogen** in the colon.

## 13. Excretion pathway 1

A part of the urobilinogen is reabsorbed into the blood and then converted to a yellow pigment, the so-called **urobilin**, in the kidney. It is then excreted with the urine.

## 14. Excretion pathway 2

With the feces, the major part of urobilinogen is excreted as **stercobilin** (brown pigment), which gives the feces its characteristic color.

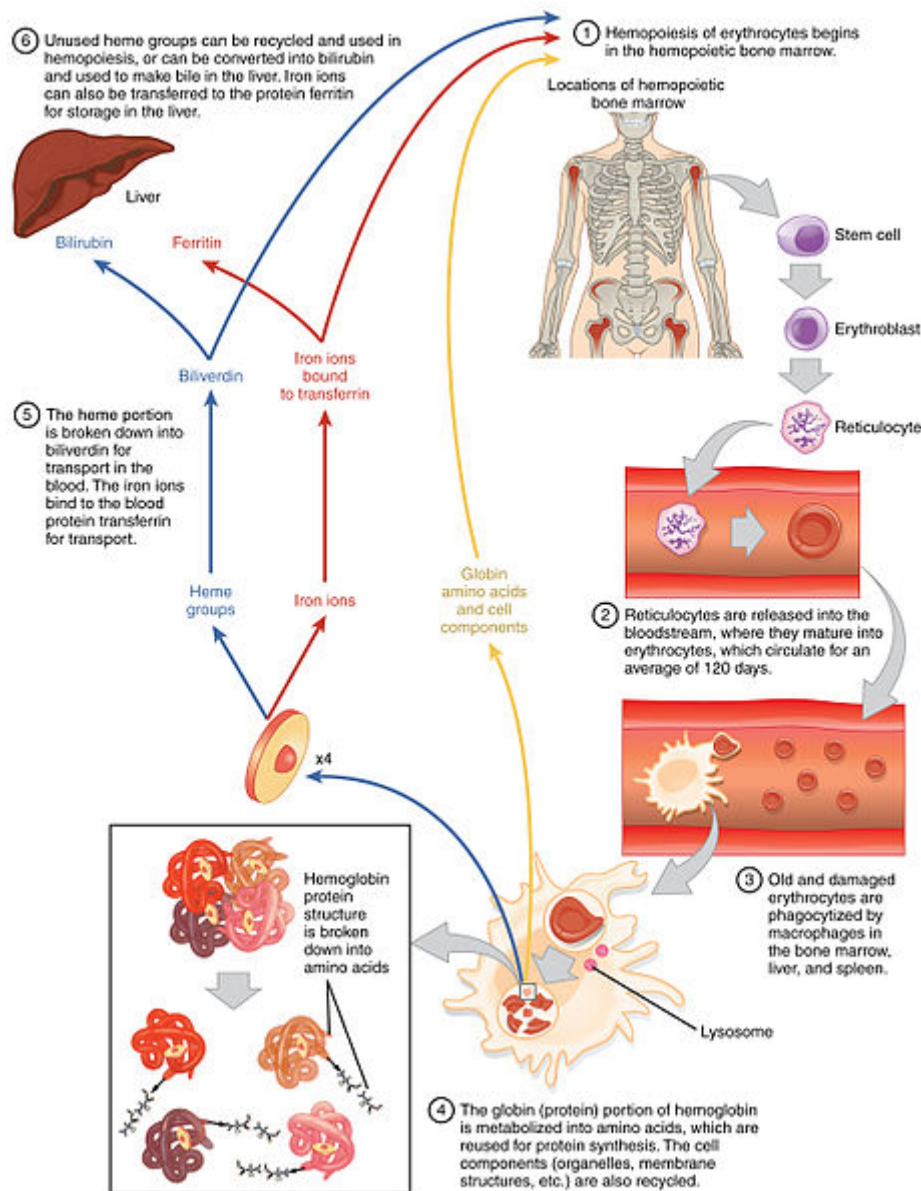


Image: Life-cycle of erythrocytes. By OpenStax College, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

## Blood Types and Basics of Transfusion Medicine

A genetically determined set of **antigens** composed of **glycoproteins** and **glycolipids** is located on the surface of the erythrocytes. These antigens also referred to as **agglutinogens**, occur in different, characteristic combinations; they are inherited together and form a blood type system. Within this blood type system, different blood types are distinguished. They differ from each other by the presence or absence of the different antigens.

About 24 blood type systems and more than 100 antigens on erythrocytes' surface are known by now. The AB0-system is 1 of the most widely used blood type systems.

### AB0-system

The AB0-system is based on 2 glycolipid-antigens (A and B).

**Note:**

Blood type A = individuals whose erythrocytes ONLY have the antigen A.

Blood type B = individuals whose erythrocytes ONLY have the antigen B.

Blood type AB = individuals whose erythrocytes have the antigen A AND B.

Blood type 0 = individuals whose erythrocytes have NONE of the 2 antigens.

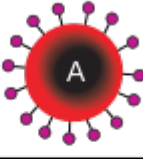
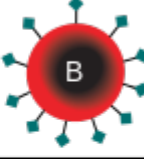
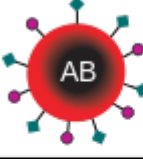
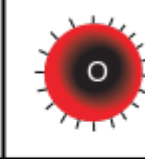



	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in Red Blood Cell	A antigen	B antigen	A and B antigens	None

Image: Blood type (or blood type) is determined, in part, by the ABO blood type antigens present on red blood cells. By InvictaHOG, License: [Public domain](#)

Antibodies, which can react with the A- or B-antigens, are usually found in the blood plasma. A person with blood type B already has the mentioned B-antigens on the erythrocytes and anti-A-antibodies in the blood plasma. However, a person with blood type 0 has both anti-A- and anti-B-antibodies in his plasma.

Only a few months after birth, the antibodies appear in the blood. The reason for their existence is not yet clear. Probably, they are produced as a result of a reaction to surface antigens of bacteria that normally live in the GI tract.

Only in very rare cases does an ABO-incompatibility between mother and fetus cause problems since the antibodies are large immunoglobulin M (IgM)-antibodies, which cannot pass the placenta.

For further differentiation of the characteristics of blood, there is the **Rhesus system**, which comprises more than 50 features. Whether the blood type is called rhesus positive = Rh+ (D) or rhesus negative = Rh- (D) depends on the presence of 1 of those 50 features, which is named with the letter D.

Anti-D-antibodies are normally not found in the blood plasma. However, a person with Rh- blood starts the production of anti-D-antibodies after a transfusion with Rh+ blood. These antibodies remain in the blood so that **agglutination** can occur if the 2nd transfusion with Rh+ blood is given due to the previously produced anti-D-antibodies. Also, hemolysis of the erythrocytes and severe, even lethal consequences can be caused by this.

## Transfusions

Blood is the tissue of the human organism that is most easily 'transplanted', despite the differences in the erythrocyte antigens. Each year, blood transfusions save many lives. A

transfusion is described as the transfer of blood or blood components (only blood plasma or erythrocytes) into the bloodstream or into the red bone marrow.

Blood is transfused for the following purposes:

- Abatement of anemia
- Increasing blood volume (e.g., after trauma with severe blood loss)
- Improvement of the immune status

### Transfusion-related problems

However, severe **antigen-antibody reactions** can be triggered in the recipient as a result of transfusion.

In the case of incompatible blood transfusions, the antibodies in the plasma of recipient bind the antigens to the transferred erythrocytes, which leads to **agglutination** of the erythrocytes. Agglutination is an antigen-antibody reaction where the RBCs interlink or clump.

The formation of the antigen-antibody complexes activates plasma proteins of the complement system. The complement molecules make the plasma membrane of the RBCs become permeable and cause **hemolysis** of the erythrocytes. During this process, hemoglobin is released into the blood plasma, which can lead to kidney damage by clogging the filtration membranes. The acute immune response often leads to a life-threatening anaphylactic shock.

If a person with blood type 'A' receives a blood donation of the type 'B', a life-threatening situation can occur.

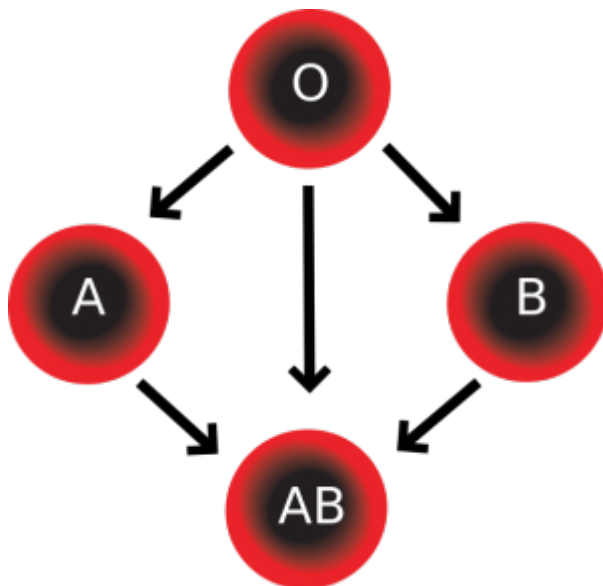


Image: Blood compatibility. By InvictaHOG, License: [Public domain](#)

However, the anti-A-antibodies in the plasma of the donator can also bind the A-antigens to the erythrocytes of the recipient. This triggers a less severe reaction because the anti-A-antibodies of the donator are strongly diluted in the plasma of the recipient. Mostly, it does not cause agglutination and hemolysis of the recipient's erythrocytes.

**Note:** A-blood should be typed and controlled before each transfusion. Also, only blood from the same blood group should be transfused. Especially in emergency situations, it

can, however, be necessary to deviate from this principle.

People with blood type 0 are referred to as 'universal donors' since they have neither anti-A- nor anti-B-antigens on their erythrocytes. Theoretically, their blood can be transfused to persons with all the other blood types.

People with the blood type AB are referred to as 'universal recipients' since they have neither anti-A- nor anti-B-antibodies in their blood plasma and are compatible with all 4 blood types.

## Hemostasis – Arrest of Bleeding

Hemostasis is a sequence of reactions that stop bleeding and trigger a hemostatic response in case of a lesion or rupture of the blood vessel. This response inhibits hemorrhage (loss of great amounts of blood out of the vessels).

In this context, 3 steps can be distinguished, which can be classified into primary and secondary hemostasis and combine with each other.

### Primary hemostasis (thrombus formation)

The primary hemostasis includes the steps of vessel reaction and the formation of a thrombus from thrombocytes (blood platelets), which stop the bleeding after approx. 1-3 minutes.

The smooth muscles in the walls of the arteries or arterioles immediately contract in case of a lesion and reduce the blood loss for several minutes or even hours, while the other hemostatic mechanisms start to operate. This reaction is also called **vasoconstriction** (vasospasm).

The thrombus formation from a thrombocyte occurs like this:

1. The thrombocytes get into contact with parts of the damaged blood vessel and stick to them. This process is called **adhesion**.
2. Through this process of adhesion, the thrombocytes are activated and develop numerous processes. As a result, they interlink, interact, and release the contents of their vesicles (adenosine diphosphate (ADP), thromboxane A<sub>2</sub>, and serotonin). This phase is called **the release reaction** of the blood platelets.
3. The release of ADP causes other blood platelets (freshly recruited) in this area to become sticky and to attach to the originally activated platelets. This accumulation of thrombocytes is referred to as **blood platelet aggregation**. A mass is formed because of the accumulation of thrombocytes, which is called platelet clot or **white thrombus**.



**Image:** Aggregation of thrombocytes (=platelets) after addition of ADP. Platelet-rich human blood plasma (left vial) is a turbid liquid. Upon addition of ADP, platelets are activated and start to aggregate, forming white flakes. By Steffen Dietzel, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

In the left tubule, there is a dull fluid, human blood plasma. By adding ADP, the thrombocytes are activated so that clots or white flakes form (right tubule).



The white thrombus very successfully inhibits blood loss in a small blood vessel. However, it is not a final closure of the bleeding site.

## Secondary hemostasis (blood coagulation)

Through blood **coagulation**, the final arrest of the bleeding is achieved. The process of coagulation is the outcome of chemical reactions which peak in the formation of fibrin filaments.

For the blood not to coagulate too quickly or too slowly, blood coagulation requires several substances known as coagulation factors. Those factors include calcium ions, different inactive enzymes, and several molecules associated with the thrombocytes or released by the damaged tissue. They are numbered with Roman numerals.

Coagulation is a very complex cascade of enzymatic reactions which eventually leads to the formation of a great amount of fibrin and can be divided into **3 stages**.

1. Two pathways—the extrinsic and intrinsic pathway—which lead to the formation of the **prothrombin activation complex**.
2. The prothrombin activator complex converts the prothrombin into the enzyme **thrombin**.
3. Thrombin converts soluble fibrinogen into the insoluble **fibrin**, which builds the filaments of the clot.

### Extrinsic pathway

The extrinsic pathway is activated very quickly within a few seconds after a severe injury. The formation of the prothrombin activator complex is stimulated by a tissue protein (tissue factor), which allows the blood from the cells outside of the blood vessel.

Tissue factor, also called **TF** or **tissue thromboplastin**, is the crucial trigger for the start of blood coagulation in the organism as it is liberated at the surface of the damaged cell. After the activation of **coagulation factor X**, it merges with coagulation factor V in the presence of **Ca<sup>2+</sup>** to form the active **prothrombin activator complex**.

### Intrinsic pathway

The intrinsic pathway of blood coagulation is slightly more complex than the extrinsic 1 and lasts longer, mostly several minutes.

If endothelial cells are damaged, the blood comes into contact with the collagenous fibers of the connective tissue around the endothelium of the blood vessels. Also, a lesion of the endothelial cells leads to damaged thrombocytes, which then release phospholipids. The **coagulation factor XII** is activated by contact with the collagenous fibers, which leads to a sequence of reactions and finally to the activation of **factor X**. Just like in the extrinsic pathway, factor X merges with **factor V** forming the active prothrombin activator complex.

### Conversion of thrombin and formation of fibrin filaments

The beginning of the common pathway of blood coagulation is the formation of the prothrombin activator complex. Then, the prothrombin activator complex catalyzes the conversion of prothrombin into thrombin in the presence of **Ca<sup>2+</sup>**. After that, **thrombin** converts the soluble **fibrinogen** into loose, but insoluble fibrin filaments with the help of **Ca<sup>2+</sup>**.

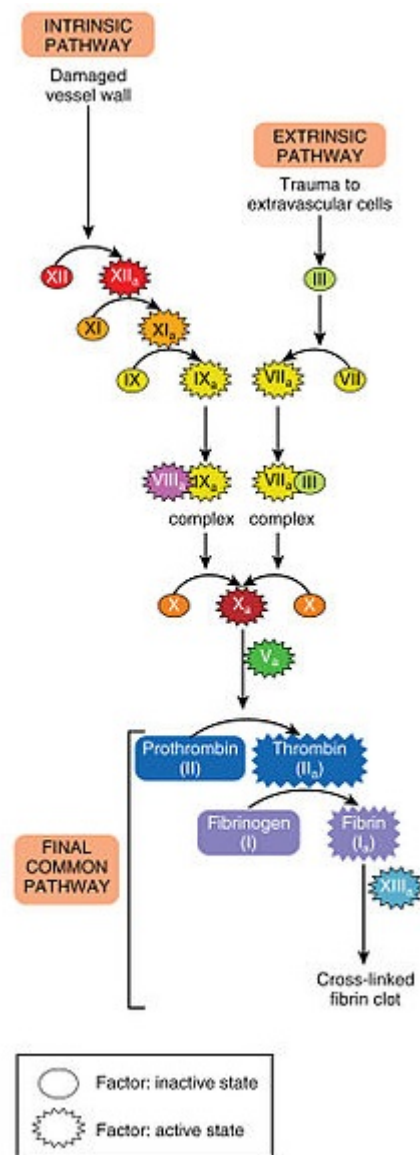
Factor XIII is activated by thrombin. It reinforces the fibrin filaments and stabilizes them to a firm clot.

## Contraction of the coagulum

The contraction of the coagulum is also called **consolidation** or solidification of the fibrin clot. The interconnected fibrin filaments contract step by step at the damaged surface of the blood vessel when thrombocytes pull on them until the ends of the damaged vessel connect.

A normal contraction depends on an appropriate amount of thrombocytes in the clot since they release the coagulation factor XIII and other factors that reinforce and stabilize the coagulum.

In wound healing, a permanent repair of the blood vessel occurs. It occurs after completion of hemostasis and is performed by **fibroblasts** producing new connective tissue in the damaged area as well as new epithelial cells, which repair the vessel lining.



(b) Fibrin synthesis cascade

Image: Blood clotting. By OpenStax College, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/), modified by Lecturio

**Note:** An appropriate amount of vitamin K is necessary for normal blood coagulation since it is vital for the synthesis of 4 coagulation factors (II, VII, IX, X).

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