In a multicellular organism, most cells cannot migrate to obtain oxygen or to eliminate carbon dioxide. The blood and the interstitial fluid fulfill these tasks. Blood consists of roughly 45% solid elements, the blood corpuscles (erythrocytes, leukocytes, and thrombocytes), and of 55% solute substances (water, proteins, etc.), the blood plasma. Here, you get a compact 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, also called erythrocytes, have a diameter of about 7 - 8 micrometers, a simple structure, and—like all other blood corpuscles—originate from a pluripotent bone marrow stem cell.

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 for why erythrocytes are highly specialized is the fact that they do not have mitochondria. Thus, they produce ATP anaerobically, i.e., without oxygen. This way, they do not use any of the oxygen it’s transporting.

Their special shape as a biconcave disc allows them to have much larger surface for diffusion of gas molecules into and out of the red blood cells than, e.g., a sphere would
have. Furthermore, their shape is indispensable for deformation of the erythrocytes when flowing through the narrow capillaries.

Each red blood cell 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⁺)**, which is located in the center of the heme ring and can reversibly bind oxygen

![Hemoglobin molecule](image)

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⁺) 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 red blood cells 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 poorly deformable erythrocytes.

2. Separation

From the hemoglobin, globin and heme components are separated.

3. Decomposition

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

4. Transferrin

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

5. Ferritin

The Fe\textsuperscript{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\textsuperscript{3+} is again coupled with transferrin.

7. Bone marrow and hemoglobin synthesis

The Fe\textsuperscript{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, red blood cells are produced in the bone marrow and then enter 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 I
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 II
With the feces, the major part of urobilinogen is excreted as stercobilin (brown pigment), which gives the feces its characteristic color.
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 one of the most widely used blood type system.

AB0-system

The AB0-system is based on two 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 two antigens

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group AB</th>
<th>Group O</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="" /></td>
<td><img src="image2.png" alt="" /></td>
<td><img src="image3.png" alt="" /></td>
<td><img src="image4.png" alt="" /></td>
</tr>
</tbody>
</table>

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 of their existence is not yet clear. Probably, they are produced as a result of reaction to surface antigens of bacteria which normally live in the gastrointestinal tract.

Only in very rare cases does an AB0-incompatibility between mother and fetus cause problems since the antibodies are large 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 one 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 production of anti-D-antibodies after a transfusion with Rh⁺ blood. These antibodies remain in the blood so that agglutination can occur if a second 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 of 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 blood stream 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 recipient as a result of transfusion.

In case of incompatible blood transfusions, the antibodies in the plasma of recipient bind the antigens to the transferred erythrocytes, that leads to **agglutination** of the erythrocytes. Agglutination is an antigen-antibody reaction where the red blood cells 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 red blood cells 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 the blood type ‘A’ receives a blood donation of the type ‘B’, a life-threatening situation can occur.

![Blood Compatibility](image.png)

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 four blood types.

Hemostasis – Arrest of Bleeding

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

In this context, three 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 approximately 1 to 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. Via 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 (ADP, thromboxane A2, and serotonin). This phase is called 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 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

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 lead 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^{2+}** to form the active **prothrombin activator complex**.

**Intrinsic Pathway**

The intrinsic pathway of blood coagulation is slightly more complex than the extrinsic one 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 the 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^{2+}**. After that, **thrombin** converts the soluble **fibrinogen** into loose, but insoluble fibrin filaments with the help of **Ca^{2+}**.

Factor XIII is also 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 which 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.

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

Solutions can be found below the sources.

1. A person with blood type A \textit{rh}^{-} can receive a transfusion from which of the following blood types?
   
   A. AB \textit{Rh}^{+}
   B. 0 \textit{rh}^{-}
   C. B \textit{rh}^{-}
   D. AB \textit{rh}^{-}
   E. \textit{Rh}^{+}

2. What happens with the iron (Fe$^{3+}$) that is released during the degradation of damaged erythrocytes?
   
   A. It is used for protein synthesis.
   B. It is transported to the liver, where it becomes a component of bile.
   C. It is used by bacteria in the gastrointestinal tract for the conversion of bilirubin to stercobilinogen.
   D. It is bound to transferrin and transported into the bone marrow, where it is used for hemoglobin synthesis.
   E. It is transformed to urobilin and excreted with the urine.

Which of the following substances is not necessary for blood coagulation?

A. Prostacyclin
B. Calcium
C. Fibrinogen
D. Vitamin K
E. Plasmin

References


http://doi.org/10.1007/978-1-4615-3796-0

http://doi.org/10.1093/jama/9780195176339.022.484

Correct answers: 1B, 2D, 3A

Legal Note: Unless otherwise stated, all rights reserved by Lecturio GmbH. For further legal regulations see our legal information page.