Hematology lecture number 3 مدرس المادة د.نوران جميل

Classification of hemoglobin

Normal hemoglobin is of various types depending on its function and the age of human.

Hemoglobin is the iron-containing protein compound within red blood cells that carries oxygen throughout the body. It is made up of heme, which is the iron-containing portion, and globin chains, which are [proteins](https://labtestsonline.org/glossary/protein/). The globin protein consists of chains of amino acids, the "building blocks" of proteins. There are several different types of globin chains, named alpha, beta, delta, and gamma. Normal hemoglobin types include:

* Hemoglobin A (Hb A): makes up about 95%-98% of hemoglobin found in adults; it contains two alpha (α) chains and two beta (β) protein chains.
* Hemoglobin A2 (Hb A2 ): makes up about 2%-3% of hemoglobin found in adults; it has two alpha (α) and two delta (δ) protein chains.
* Hemoglobin F (Hb F, fetal hemoglobin): makes up to 1%-2% of hemoglobin found in adults; it has two alpha (α) and two gamma (γ) protein chains. It is the primary hemoglobin produced by the fetus during [pregnancy](https://labtestsonline.org/understanding/wellness/pregnancy/); its production usually falls shortly after birth and reaches adult level within 1-2 years.
* Embryonic hemoglobin produced in the [blood islands](https://en.wikipedia.org/wiki/Blood_islands) in the embryonic [yolk sac](https://en.wikipedia.org/wiki/Yolk_sac) during (first week of pregnancy until the end of the pregnancy). The protein is commonly referred to as Hemoglobin ε. **Blood islands** are structures around the developing [embryo](https://en.wikipedia.org/wiki/Embryo) which lead to many different parts of the circulatory system. Blood islands arise external to the developing embryo on the [umbilical vesicle](https://en.wikipedia.org/wiki/Umbilical_vesicle), [allantois](https://en.wikipedia.org/wiki/Allantois), [connecting stalk](https://en.wikipedia.org/wiki/Connecting_stalk) and [chorion](https://en.wikipedia.org/wiki/Chorion)

The quantity of the hemoglobin that is produced depends on the stage of human development. Fetal hemoglobin predominates whilst a baby is in the womb but it will start to make a small proportion of the adult type hemoglobin before birth. By the time a child is one year old there is a switch over in the amount of Fetal and Adult type hemoglobin produced. If a child has inherited normal hemoglobin the quantity produced at birth and throughout adulthood is indicated below:

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| **Hemoglobin** | **Newborn** | **Age above one Year Old and throughout Adulthood** |
| Hemoglobin F | 95% | <1% |
| Hemoglobin A | 5 – 10% | >95% |
| Hemoglobin A2 | 2.2 - 3.5% | 2.2 - 3.5% |

Genetic changes ([mutations](https://labtestsonline.org/glossary/mutation/)) in the globin [genes](https://labtestsonline.org/glossary/gene/) cause alterations in the globin protein, resulting in structurally altered hemoglobin, such as hemoglobin S, which causes [sickle cell](https://labtestsonline.org/understanding/conditions/sickle/), or a decrease in globin chain production ([thalassemia](https://labtestsonline.org/understanding/conditions/thalassemia/)). In thalassemia, the reduced production of one of the globin chains upsets the balance of alpha to beta chains and causes abnormal hemoglobin to form (alpha thalassemia) or causes an increase of minor hemoglobin components, such as Hb A2 or Hb F (beta thalassemia).

Four genes code for the alpha globin chains, and two genes (each) code for the beta, delta, and gamma globin chains.

Mutations may occur in either the alpha or beta globin genes. The most common alpha-chain-related condition is alpha thalassemia. The severity of this condition depends on the number of genes affected.

Oxygen-Carrying Protein in the Blood: Hemoglobin

Hemoglobin is the protein that transports oxygen (O2) in human blood from the lungs to the tissues of the body. Proteins are formed by the linking of amino acids into polypeptide chains. An individual amino acid in a protein is known as a "residue." The arrangement and interactions of the amino-acid residues within the protein determine the protein's shape and contribute substantially to its function. Hemoglobin is a globular protein (i.e., folded into a compact, nearly spherical shape) and consists of four subunits, as shown in Figure 2. Each protein subunit is an individual molecule that joins to its neighboring subunits through intermolecular interactions. (These subunits are also known as peptide chains. these subunits are also known as peptide chains.

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| **Figure 2**  This is a molecular model of hemoglobin with the subunits displayed in the ribbon representation. A ribbon representation traces the backbone atoms of a protein and is often used to represent its three-dimensional structure. The four heme groups are displayed in the ball-and-stick representation. |

**the Protein Subunit**

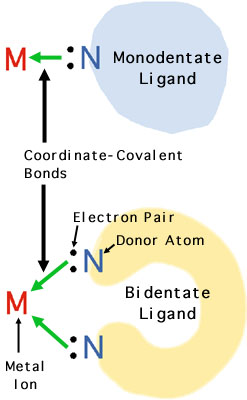
Each subunit in Figure 2 contains regions with a coiled shape; many of the amino acids that make up the polypeptide chain interact to form this particular structure, called an alpha helix. In an alpha helix (Figure 3), each amino acid is "hydrogen-bonded" to the amino acid that is four residues ahead of it in the chain. In hemoglobin, the hydrogen-bonding interaction occurs between the H of an -NH group and the O of a -CO group of the polypeptide backbone chain; the amino-acid side chains extend outward from the backbone of the helix. Approximately 75% of the amino-acid composition of hemoglobin adopts an alpha-helical structure. Another common structural motif is the beta-pleated sheet, in which amino acids line up in straight parallel rows. .

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| **Figure 3**  This is a molecular model of the alpha-helix structure in a subunit of hemoglobin. The blue strands are a ribbon representation to emphasize the helical structure. The green dotted lines show the hydrogen bonding between the -NH and -CO functional groups. |

**The Heme Group**

In hemoglobin, each subunit contains a heme group, which is displayed using the ball-and-stick representation in Figure 2. Each heme group contains an iron atom that is able to bind to one oxygen (O2) molecule. Therefore, each hemoglobin protein can bind four oxygen molecules.

One of the most important classes of chelating agents in nature are the porphyrins. A porphyrin molecule can coordinate to a metal using the four nitrogen atoms as electron-pair donors, and hence is a polydentate ligand (see Figure 1).



**Figure 1**

You have already learned that a covalent bond forms when electrons are shared between atoms. A **coordinate-covalent bond**(represented by a green arrow in this diagram) forms when both of the shared electrons come from the same atom, called the **donor atom** (blue).

An anion or molecule containing the donor atom is known as a **ligand**. The top illustration shows a coordinate-covalent bond between a metal ion (e.g.*,* Fe, shown in red) and a **monodentate ligand** (a ligand that contains only one electron-pair-donor atom, shown in light blue). The bottom illustration shows a metal ion with coordinate-covalent bonds to a **bidentate ligand** (a ligand that contains two donor atoms simultaneously coordinated to the metal ion, shown in yellow).

Heme is a porphyrin that is coordinated with Fe(II) and is shown in Figure 4.

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| **Figure 4**  On the left is a three-dimensional molecular model of heme coordinated to the histidine residue (a monodentate ligand, see Figure 1) of the hemoglobin protein. On the right is a two-dimensional drawing of heme coordinated to the histidine residue, which is part of the hemoglobin protein.  **Note:**The coordinate-covalent bonds between the central iron atom and the nitrogen from the porphyrin are gold; the coordinate-covalent bond between the central iron atom and the histidine residue is green. In the three-dimensional model, the carbon atoms are are gray, the iron atom is dark red, the nitrogen atoms are dark blue, and the oxygen atoms are light red. The rest of the hemoglobin protein is purple.   |  |  | | --- | --- | |  |  | | |