

HAEMOGLOBIN: STRUCTURE, PROPERTIES AND BIOMEDICAL FUNCTIONS

Hemoglobin is the iron-containing oxygen-transport metalloproteins in the red cells of the blood in mammals and other animals. A spheroidal heme protein having four subunits each consisting of a globular protein non-covalently bound, with an embedded heme group. Hb has a molecular weight of about 64456. The globular protein units of Hb is made up of two identical pairs of polypeptide chains, i.e. two identical alpha (α) chains containing 141 amino acids and two identical non- α chains (beta(β), gamma(γ), delta(δ) or epsilon (ϵ) chains. In adult humans the non- α chains are beta (β), containing 146 amino acids. This is denoted as $\alpha_2\beta_2$ and termed hemoglobin A. The combination of two alpha chains and two gamma chains form fetal hemoglobin, termed hemoglobin F. The product of the delta globin gene is called hemoglobin A2

The different kinds of chains are encoded for by different genes. The genes that encode the alpha globin chains are on chromosome 16 (Figure 2). Those that encode the non-alpha globin chains are on chromosome 11 in humans.

The pairing of one alpha chain and one non-alpha chain produces a hemoglobin dimer (two chains). The hemoglobin dimer does not efficiently deliver oxygen, however. Two dimers combine to form a hemoglobin tetramer, which is the functional form of hemoglobin.

The heme group consists of an iron atom held in a heterocyclic ring, known as a porphyrin. This iron atom is the site of oxygen binding. The iron atom binds equally to all four nitrogen atoms in the center of the ring, which lie in one plane. Oxygen is then able to bind to the iron centre perpendicular to the plane of the porphyrin ring while the last position is used to form a coordinate covalent bond with the side chain of a single histidine amino acid of the protein, called the proximal histidine.

STRUCTURE

Hb is largely alpha-helical; each chain contains helical segments between which are short non coiled segments. The chains are wound round itself to form a pocket in which the heme group nestles and this pocket is usually formed by hydrophobic amino acids.

FUNCTIONS

1. Hb binds and transports oxygen from the lungs to tissues.
2. It also transports CO₂ from tissues to lungs.
3. It acts as a buffer, by transporting protons as Hb.2H⁺.

HAEMOGLOBINOPATHIES: HBS, THALASSAEMIAS, HEMOPHILIA

HEMOGLOBINOPATHIES.

These are disorders in the structure of Hb resulting in altered biologic function as a result of defects in the genes that code for one or more of the globin chains. More than 700 structural variants of Hb have been described in man and animals.

Hbopathies can occur as a result of point mutations in the DNA code for globin chains, others as a result of deletions of extensive portions of the globin genomes or as a result of insertion of single or double nucleotides, inversions or substitution.

Defects in Hb can occur in one of three circumstances;

1. Structural defects in the Hb molecule as a result of mutations in the globin gene
2. Diminished production of one of the globin subunits- this mutational change results in a condition called thalassemias.
3. Abnormal association of the otherwise normal subunits e.g. all four subunits being solely α or β chains.

HbS

Is a classical example of Hbopathies that occurs in humans where the two α chains are normal but one of the β chains has a mutation which is a single base substitution reflected at the level of the sixth amino acid, where an adenine nucleotide is replaced by thymine giving a GTG codon (for valine) instead of a GAG (for glutamic acid) which is found in HbA the normal hemoglobin.

This single amino acid substitution causes a considerable change in the structure of the entire Hb molecule by causing a protrusion that accidentally fits into a complementary site on the β chain of the next Hb molecule hence the Hb molecules hook together, are collapsed and result in a sickle shaped, rigid RBC i.e. the Hb lies along like fibres in the RBC instead of being globular, Valine is less polar than glutamic acid, and most hydrophobic amino acids aggregate together internally and expose the hydrophilic (polar) ones to react with water.

Thus the RBCs with such sickle shape are unable to carry oxygen adequately especially if the oxygen tension is low, but when the oxygen tension is high, the Hb molecules depolymerize and return to a normal state but this only for a short duration.

This Hb defect results in a condition known as sickle cell disease and is mainly characterized by anemia, weakness etc.

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