Haemoglobin and the Haemoglobinopathies

Haemoglobin and myoglobin

The main oxygen transport proteins in humans are haemoglobin and myoglobin. Haemoglobin arose from myoglobin through the ages. Their main difference is that hemoglobin consists of four oxygen binding sites and myoglobin has one. Haemoglobin is responsible protein for oxygen transport through the blood stream and is present in red blood cells (erythrocytes) where as myoglobin is present in muscle cells.

Haemoglobin

There are many different types of haemoglobin. Each one has a different composition and appears during different time in life. Every haemoglobin consist of four globin chains two of which are identical . together they form a tetramer . Each of these chains is attached on a heme group with an oxygen binding site. Haemoglobins differ in the arrangement of their chains. We have three main types of haemoglobin molecules.

- HbA (haemoglobin a) consists of 2 α and 2 β chains , this is the main haemoglobin present in adults. (α chain 140 Amino acids , β chain 146 amino acids) 97-98%
- HbA2 (haemoglobin a2) consists of 2 α and 2 δ chains , this haemoglobin is present in adults in a very small proportion. 2-3% (only difference between HbA and HbA2 is that the latter has different electrophoretic mobility)
- HbF (fetal haemoglobin) consists of 2 α and 2 γ chains , this type is being produced during fetal period.<1%

During embryonic development 3 main types of haemoglobin exist :

- Hb Gower 1 consists of 2 ζ chains and 2 ε chains
- Hb Gower 2 consists of 2 α chains and 2 ε chains
- Hb Portland consists of 2 ζ chains and 2 γ chains

Note: ζ chains resemble α chains and are sometimes called α-like but ε+γ chains resemble β chains and are sometimes called β-like

The Haemoglobinopathies

Can be divided into two groups:

1. Disorders of production of the globin chains which leads to thalassemias
2. Structural variation of globin chains can lead to diseases like sickle cell anaemia

The Thalassemias

Derived from the Greek word for sea (=θαλασσα) because of it's common occurrence in the Mediterranean. They are an inherited disease (AR) and are clasified based on the globin chain whic is either not beeing produced or is showing decreased production. Based on the chain being under produced we name the Thalassemia. For example lack of α-globin chain is observed in α-Thalassemia. The Thalassemias are divided into two groups:

- α-Thalassemia
- β-Thalassemia

α-Thalassemia

This Thalassemia results from deficiency in α-globin. There are four different types of α-Thalassemia apart from the normal healthy person . Since the production of α-globin is controled by 4 genes (2 maternal + 2 paternal) on chromosome 16 (short arm p) based on how many of them are missing we have and the apropriate phenotype. Each one differing in severity.

- The normal healthy person has all of his 4 α globin genes functioning. So the ratio of α-globin to β-globin is 1:1.
- When a person has 3 of his 4 genes active and producing α-globin we say that he is a silent carrier. No effect on persons life or phenotype. Ratio of α-globin to β-globin is 0.8:1
- When a person has half of his globin genes missing or not working properly we say he has the α-Thalassemia trait. In this case we have two possible genotypes . First one is that the 2 genes are missing form the same chromosome(sis) we call it Thal-1 and if the two missing genes are from different chromosomes (trans) we call it Thal-2 . Patients carrying the thalassemia trait show mild anemia. Ratio of α-globin to β-globin is 0.6:1
- When only one of the genes is active is when the thalassemia gets severe. In this case due to the fact that the ratio of α-globin to β-globin is down to 0.3:1 a teramer between β-globin chains called HbH (β4) is formed. HbH has an oxygen affinity like myoglobin and does not release oxygen normally in tissues and organs. HbH is also prone to crystallization and causes haematolysis in red blood cells.

- The most severe form of α-Thalassemia is whren no functional gene is present. This is called Hyprops Fetalis. Due to no production of α-globin this leads to severe anaemia , edema , heart failure and death in utero or shortly after birth.

β-Thalassemia

Is the underproduction of β-globin chains. It is rarely cased by a deletion is most commonly based due to a mutation of a DNA. There are six main types of mutations that cause β-Thalassemia

- Transcription mutations: can lead to reduced production of β-globin chains
- mRNA splicing mutations
- Polyadenylation signal mutations : mutations in the 3' end of the globin gene can cause the untranslated transcript not to be polyadenylated.
- RNA modification mutations : can lead to reduced translation and reduced profuction
- Chain termination mutations : alterations on a single nucleotide can lead to stop codon leading to a shortened chain .
- missense mutations :can lead to unstable β-chains

Three types of β-Thalassemia:

1. Thalassemia minor : caused by mutation on one β-globin gene and it is asymptomatic
2. Thalassemia intermedia : quite more severe than minor and requires occaisonal transfusions
3. Thalassemia major : cased by mutation on both β-globin genes. Transfusion dependant

Sickle cell disease

Autosomal recessive and one of the most common haemoglobinopathy, results form a monozygosity of a mutation in a β-globin gene. Sickle cell anemia can lead to renal failure, pericaditis and heart failure, and weakness mostly in limbs and spine. A characteristic sign of sickle cell disease is the morphology of the red blood ceels under the microscope. The cells curved (sickle), where the disease name comes from. For future reference we will call the affected haemoglobin HbS as appointed by Dr. Paulin 1949. This HbS polymerizes in the red blood cells causing the change in shape. Also HbS has a lower solubility than HbA which in turn causes blood viscosity to increase and leads to clumping of cells. This is due to Glutamic acid beeing replaced by Valine. Valine is a hydrophobic amino acid and this is the reason for the lowered solubility. HbS in the deoxy state (not carrying oxygen) tends to crystallize and forms rods which clog small arteries which lead to oxygen shortage in specific tissues. Red blood cells that are damaged beyond repair and cannot function correctly any more are removed from circulation. This leads to the need for faster production of red blood cells to compensate for the removed numbers. The cells due to their curved shape they have the tendency to to block small arteries which leads to less oxygen reaching the specific tissues. Patients suffering from sickle cell disease have a shorter life expectancy than the general population. Early recognition of the disease can lead to prolongation of life.

Sickle cells disease and malaria

Based on the findings of A.C.Alison in 1954 it was found that patients heterozygous to the sickle cell disease have a form of protection against the parasite of malaria and are less severely affected. TURNPENNY, Peter. *Emery's elements of medical genetics.* 13th edition. 2008. ISBN 987-0-7020-2917-2.

PASSARGE, Eberhard. *Colour atlas of genetics.* 3rd edition. 2007. ISBN 978-3-13-100363-8.