Sickle Cell Anemia

The sickle cell mutation reflects a single change in the amino acid building blocks of the oxygen-transport protein, hemoglobin. This protein, which is the component that gives red cells their color, has two subunits. The alpha subunit is normal in people with sickle cell disease. The beta subunit has the amino acid valine at position 6 instead of the glutamic acid that is normally present. The alteration is the basis of all the problems that occur in people with sickle cell disease. The schematic diagram shows the first eight of the 146 amino acids in the beta globin subunit of the hemoglobin molecule. The amino acids of the hemoglobin protein are represented as a series of linked, colored boxes. The lavender box represents the normal glutamic acid at position 6. The dark green box represents the valine in sickle cell hemoglobin. The other amino acids in sickle and normal hemoglobin are identical.

Schematic Represntation of the Amino Acid Substitution in Sickle Cell Disease

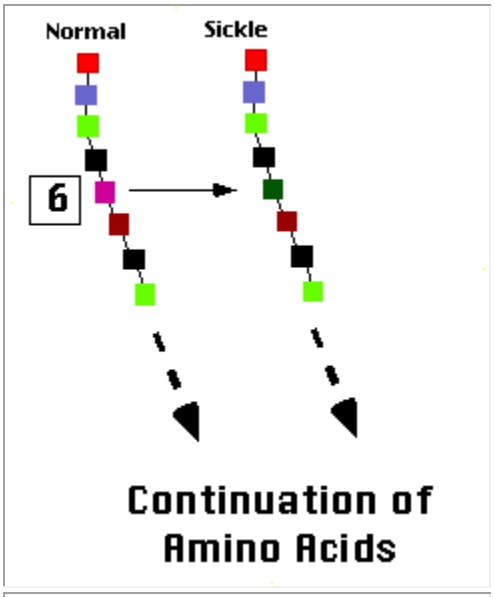

Figure 1. The chain of colored boxes represent the first eight amino acids in the beta chain of hemoglobin. The sixth position in the normal beta chain has glutamic acid, while sickle beta chain has valine. This is the sole difference between the two.

The molecule, DNA (deoxyribonucleic acid), is the fundamental genetic material that determines the arrangement of the amino acid building blocks in all proteins. Segments of DNA that code for particular proteins are called genes. The gene that controls the production of the beta globin subunit of hemoglobin is located on one of the 46 human chromosomes (chromosome #11). People have twenty-two identical chromosome pairs (the twenty-third pair is the unlike X and Y chromosomes that determine a person's sex). One of each pair is inherited from the father, and one from the mother. Occasionally, a gene is altered in the exchange between parent and offspring. This event, called mutation, occurs extremely rarely. Therefore, the inheritance of sickle cell disease depends totally on the genes of the parents.

If only one of the beta globin genes is the "sickle" gene and the other is normal, the person is a carrier for sickle cell disease. The condition is called sickle cell trait. With a few rare exceptions, people with sickle cell trait are completely normal. If both beta globin genes code for the sickle protein, the person has sickle cell disease. Sickle cell disease is determined at conception, when a person acquires his/her genes from the parents. *Sickle cell disease cannot be caught, acquired, or otherwise transmitted.* Also, sickle cell trait does not develop into sickle cell disease. Sickle cell trait partially protects people from the deadly consequences of malaria. The frequency of the sickle cell gene reached high levels in Africa and India due to the protection against malaria that occurred for people with *sickle cell trait*.

Oxygen and the Formation of Polymers of Sickle Hemoglobin

The hemoglobin molecule (made of alpha and beta globin subunits) picks up oxygen in the lungs and releases it when the red cells reach peripheral tissues, such as the muscles. Ordinarily, the hemoglobin molecules exist as single, isolated units in the red cell, whether they have oxygen bound or not. Normal red cells maintain a basic disc shape, whether they are transporting oxygen or not.

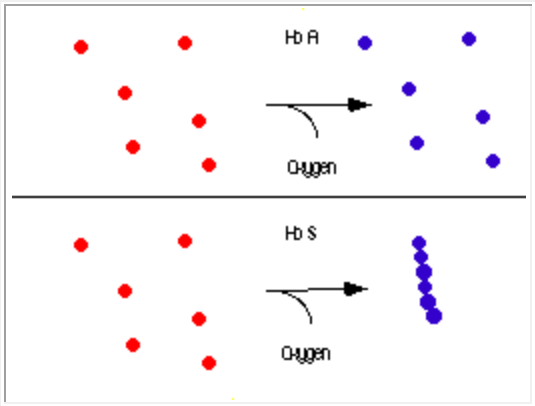

Figure 2. Normal hemglobin exists as solitary units whether oxygenated or deoxygenated (upper panel). In contrast, sickle hemoglobin molecules adhere when they are deoxygenated, forming sickle hemoglobin polymers (lower panel).

The picture is different with sickle hemoglobin (Figure 2). Sickle hemoglobin exists as isolated units in the red cells when they have oxygen bound. When sickle hemoglobin releases oxygen in the peripheral tissues, however, the molecules tend to stick together and form long chains or polymers. These rigid polymers distort the cell and cause it to bend out of shape. While most distorted cells are simply shaped irregularly, a few have a cresent-like appearance under the microscope. These cresent-like or "sickle shaped" red cells gave the disorder its name. When the red cells return to the lungs and pick up oxygen again, the hemoglobin molecules resume their solitary existence (the left of the diagram).

A single red cell may traverse the circulation four times in one minute. Sickle hemoglobin undergoes repeated episodes of polymerization and depolymerization. This cyclic alteration in the state of the molecules damages the hemoglobin and ultimately the red cell itself.

Polymerized sickle hemoglobin does not form single strands. Instead, the molecules group in long bundles of 14 strands each that twist in a regular fashion, much like a braid (Figure 3).

Schematic Representaion of Polymerized Sickle Hemoglobin

Figure 3. Polymers of deoxygenated sickle hemoglobin

These bundles self-associate into even larger structures that stretch and distort the cell. An analogy would be a water balloon which was stretched and deformed by icicles. The stretching of the balloon's rubber is similar to what happens to the membrane of the red cell. Polymers tend to grow from a single start site (called a nucleation site) and often grow in multiple directions. Star-shaped clusters of hemoglobin S polmers develop commonly.

molecules. Each hemoglobin molecule is represented as a sphere. The spheres twist in an alpha helical bundle made of 14 sickle hemoglobin chains.

The Sickle Red Cell

Capillary Flow of Normal and Sickle Red Cells

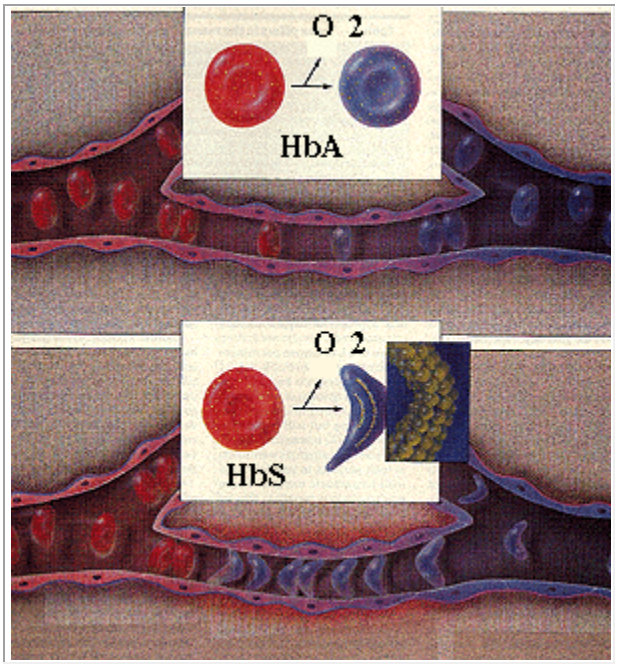

Figure 4. Normal red cells maintain their shape as they pass through the capillaries and release oxygen to the peripheral tissues (upper panel). Hemoglobin polymers form in the sickle rell cells with oxygen release, causing them to deform. The deformed cells block the flow of cells and interrupt the delivery of oxygen to the tissues (lower panel).

Figure 4 shows the changes that occur as sickle or normal red cells release oxygen in the microcirculation. The upper panel shows that normal red cells retain their biconcave shape and move through the smallest vessels (capillaries) without problem. In contrast, the hemoglobin polymerizes in sickle red cells when they release oxygen, as shown in the lower panel. The polymerization of hemoglobin deforms the red cells. The problem, however, is not simply one of abnormal shape. The membranes of the cells are rigid due in part to repeated episodes of hemoglobin polymerization/depolymerization as the cells pick up and release oxygen in the circulation. These rigid cells fail to move through the small blood vessels, blocking local blood flow to a microscopic region of tissue. Amplified many times, these episodes produce tissue hypoxia (low oxygen supply). The result is pain, and often damage to organs.

The damage to red cell membranes promotes many of the complications of sickle cell disease. Robert Hebbel at the University of Minnesota and colleagues were among the first workers to show that the heme component of hemoglobin tends to be released from the protein with repeated episodes of sickle hemoglobin polymerization. Some of this free heme lodges in the red cell membrane. The iron in the center of the heme molecule promotes formation of very dangerous compounds, called reactive oxygen species. These molecules damage both the

lipid and protein components of the red cell membrane. Membrane stiffness is one of the consequences of this injury. Also, the damaged proteins tend to clump together to form abnormal clusters in the red cell membrane. Antibodies develop to these protein clusters, leading to even more red cell destruction (hemolysis).

The anemia in sickle cell disease is caused by red cell destruction, or hemolysis. The production of red cells by the bone marrow increases dramatically, but is unable to keep pace with the destruction. Red cell production increases by five to ten-fold in most patients with sickle cell disease. The average half-life of normal red cells is about 40 days. In patients with sickle cell disease, this value can fall to as low as four days. The volume of "active" bone marrow is much greater than normal in patients with sickle cell disease due to the demand for greater red cell production.

The degree of anemia varies widely between patients. In general, patients with sickle cell disease have hematocrits that are roughly half the normal value (*e.g.*, about 25% compared to about 40-45% normally). Patients with hemoglobin SC disease (where one of the beta globin genes codes for hemoglobin S and the other for the variant, hemoglobin C) have higher hematocrits than do those with homozygous Hb SS disease. The hematocrits of patients with Hb SC disease run in low- to mid-thirties. The hematocrit is normal for people with sickle cell trait.

Sickle cell trait (or **sicklemia**) describes a condition in which a person has one abnormal allele of the hemoglobin beta gene (is heterozygous), but does not display the severe symptoms of sickle cell disease that occur in a person who has two copies of that allele (is homozygous). Those who are heterozygous for the sickle cell allele produce both normal and abnormal hemoglobin (the two alleles are co-dominant). Sickle cell disease is a blood disorder in which the body produces an abnormal type of the oxygen-carrying substance hemoglobin in the red blood cells. Sickling and sickle cell disease also confer some resistance to malaria parasitization of red blood cells, so that individuals with sickle-cell trait (heterozygotes) have a selective advantage in some environments.

Hemoglobin genetics

Normal hemoglobin is called hemoglobin A, but people with sickle cell disease have only hemoglobin S, which turns normal, round red blood cells into abnormally curved (sickle) shapes.

Normally, a person inherits two copies of the gene that produces beta-globin, a protein needed to produce normal hemoglobin (hemoglobin A, genotype AA). A person with sickle cell trait inherits one normal gene and one abnormal gene encoding hemoglobin S (hemoglobin genotype AS).

Prevalence

Sickle cell trait prevalence is highest in West Africa (25% of the population). It also has a high prevalence in South and Central Americans, especially those in Panama. However, it also very infrequently appears in Mediterranean countries such as Italy, Greece, and Spain, where it most

likely expanded via the selective pressure of malaria, a disease that was endemic to the region.[1] It has been described in Indians, Middle Easterners (such as Arabs and Iranians), Native American peoples, North Africans, and Turks.[*citation needed*]

Symptoms

Sickle cell trait is a hemoglobin genotype AS is generally regarded as a benign condition.[2] However, individuals with sickle cell trait may have rare complications. For example, in November 2010, Dr. Jeffery K. Taubenberger of the National Institutes of Health discovered the earliest proof of Sickle-cell disease while looking for the virus of the 1918 flu during the autopsy of an African-American soldier. Taubenberger autopsy results show that he suffered a sickle-cell crisis that contributed to his death even though he had one copy of the gene.[3] There have been calls to reclassify sickle cell trait as a disease state, based on its malignant clinical presentations.[4] Significance may be greater during exercise.[5]

Sickle cell trait provides a survival advantage over people with normal hemoglobin in regions where malaria is endemic. The trait is known to cause significantly fewer deaths due to malaria, especially when *Plasmodium falciparum* is the causative organism. This is a prime example of natural selection, evident by the fact that the geographical distribution of the gene (for hemoglobin S) and the distribution of malaria in Africa virtually overlap. Because of the unique survival advantage, people with the trait increase in number as more people infected with malaria and having the normal hemoglobin tend to succumb to the complications.

Although the precise mechanism for this phenomenon is not known, a several factors are believed to be responsible.

- Infected erythrocytes (Red Blood cells) tend to have lower oxygen tension, because it is significantly reduced by the parasite. This causes sickling of that particular erythrocyte, signalling the phagocytes to get rid of the cell and hence the parasite within.
- Since the sickling of parasite infected cells is higher, these selectively get removed by the reticulo-endothelial system, thus sparing the normal erythrocytes.
- Excessive vacuole formation occurs in those parasites infecting sickle cells.
- Sickle trait erythrocytes produce higher levels of the superoxide anion and hydrogen peroxide than do normal erythrocytes, both are toxic to malarial parasites.[6]

The sickle cell trait was found to be 50% protective against mild clinical malaria, 75% protective against admission to the hospital for malaria, and almost 90% protective against severe or complicated malaria.