Sickle cell disease

An inherited disorder of red blood cells characterized by lifelong anemia and recurrent painful episodes. The sickle cell mutation is caused by a single nucleotide effecting a change in the β-globin gene, resulting in the substitution of valine for glutamic acid as the sixth amino acid of β-globin. The short circulatory survival of red blood cells that contain sickle cell hemoglobin S results in anemia, and their abnormal rigidity contributes to painful obstruction of small blood vessels. See also: Anemia; Genetic code; Hemoglobin

Genetics

The sickle cell gene is found most commonly among individuals of African ancestry, but also has a significant incidence in Mediterranean, Middle Eastern, and Asian Indian populations. Its evolutionary persistence in these populations is related to its ability to partially protect heterozygous individuals from death due to malaria. The geographic dispersion of this gene is related to its having arisen as a spontaneous mutation at least four different times and to its transmission along ancient trade routes.

Inheritance of one sickle gene and one normal β-globin allele results in a simple heterozygous condition known as sickle cell trait. This benign carrier condition is associated with a normal life expectancy, and it does not cause either anemia or recurrent pain. However, carriers may occasionally experience blood in their urine and be more subject to the risk of sudden death when engaging in rigorous prolonged physical conditioning. The large amounts of hemoglobin A within sickle-cell-trait red blood cells protect against the deleterious effects of hemoglobin S. The inheritance of homozygous sickle cell anemia results in sufficiently high intracellular concentration of sickle cell hemoglobin S to cause clinical disease. See also: Human genetics

Pathophysiology

The pathophysiology of sickle cell disease has three aspects: molecular, cellular, and rheological. The property of sickle cell hemoglobin S responsible for clinical disease is its insolubility when deoxygenated. Oxygenated sickle cell hemoglobin S is as soluble as oxygenated normal hemoglobin, but when it is deoxygenated it aggregates and forms an insoluble polymer.

The effects of sickle cell hemoglobin on sickle red blood cells is catastrophic in terms of their circulatory survival and deformability. While normal red blood cells circulate for 4 months, sickle cells survive in the circulation for only about 12–20
Polymerization of sickle cell hemoglobin within deoxygenated sickle cells reversibly reduces cellular deformability and distorts cells to the sickle shape (see illustration). Sickle cells usually return from the venous circulation to the arterial, where the hemoglobin is reoxygenated and the cells unsickle. The so-called vicious cycle of erythrostasis that has been proposed to account for the episodic vascular occlusion of sickle cell disease suggests that transient stasis of blood flow results in deoxygenation of sickle cells and the generation of an acidic milieu, both of which make possible the polymerization and sickling responsible for recurrent pain and organ dysfunction. Initiation of vascular occlusion, however, appears to be the result of abnormally sticky young sickle cells adhering to the vascular endothelium.

Persistent cycles of sickling and unsickling result in the generation of dehydrated, very dense sickle cells; these are irreversibly sickled cells that are incapable of resuming a normal shape when reoxygenated. Their generation is the result of abnormal cell losses of cations and water via potassium-chloride cotransport and calcium-sensitive potassium efflux, called the Gardos pathway.

As a result of the poor deformability of individual sickle red blood cells, sickle cell blood has high viscosity. The impaired rheologic properties of sickle blood are compounded by abnormal adherence of sickle red cells to endothelial cells lining the blood vessels.

**Clinical manifestations**

The short-lived nature of sickle red blood cells results in lifelong chronic hemolytic anemia with which accelerated red blood cell production cannot keep pace. The increased turnover of red blood cells results in elevated levels of hemoglobin degradation and bilirubin production by the liver and in very frequent formation of gallstones. Individuals with sickle cell disease are also afflicted with episodes of increased severity of anemia, usually due to cessation of erythropoiesis. Vasooocclusive complications of sickle cell disease include the episodic painful crises and both chronic and acute organ dysfunction, for example, strokes, painful necrosis of bone, loss of vision, diminished function of the liver and kidneys, blood in the urine, and poorly healing ulcers of the legs. Older individuals frequently have a degree of heart failure that may be related to both anemia and vascular occlusion. Individuals with sickle cell disease are generally regarded as having severely shortened life expectancy, but survival has improved to the extent that average life expectancy is in the fifth decade. One disease manifestation that is particularly problematic in young children is susceptibility to infections. Prior to the use of prophylactic antibiotics in infants and toddlers, septicemia was the leading cause of death in this age group.
**Diagnosis**

The standard method of diagnosing sickle cell syndromes is hemoglobin electrophoresis. The replacement of negatively charged glutamic acid by neutrally charged valine results in sickle cell hemoglobin S having a different electrophoretic mobility from normal hemoglobin. On electrophoresis, the hemoglobin of subjects with homozygous sickle cell anemia is virtually all sickle cell hemoglobin, while that of individuals with sickle cell trait includes both normal and sickle cell hemoglobin. Another method of detecting sickle cell hemoglobin is solubility testing in a high-ionic-strength solution, a test that will be positive in sickle trait as well as in sickle cell disease. A simple diagnostic tool is to review the peripheral blood smear microscopically for the presence of irreversibly sickled cells. These cells are almost always found in individuals with sickle cell disease but are absent in those with sickle trait. See also: **Electrophoresis** (/content/electrophoresis/226400)

There are a variety of diagnostic tests based on deoxyribonucleic acid (DNA). These tests depend on the ability to detect substitution of the single nucleotide responsible for the sickle gene in native genomic DNA or in DNA that has been amplified enzymatically from genomic DNA using the polymerase chain reaction. These DNA-based diagnostic methods are particularly useful for prenatal diagnosis of sickle cell disease, where often only small amounts of DNA for diagnosis are obtained by amniocentesis or chorionic villus sampling. See also: **Deoxyribonucleic acid (DNA)** (/content/deoxyribonucleic-acid-dna/186500); **Prenatal diagnosis** (/content/prenatal-diagnosis/543350)

**Therapy**

Despite the profound understanding of sickle cell disease, treatment of painful episodes often consists of only symptomatic therapy, including analgesics for pain, antibiotics for infections, and transfusions for episodes of severe anemia. Previous attempts at inhibiting polymerization of sickle cell hemoglobin have been unsuccessful because of intolerable side effects or lack of beneficial effect. Genetic counseling and prenatal diagnosis remain important therapeutic approaches. See also: **Blood** (/content/blood/087600); **Genetic engineering** (/content/genetic-engineering/285000)

**Bibliography**


**Additional Readings**

J. E. Bradner et al., Chemical genetic strategy identifies histone deacetylase 1 (HDAC1) and HDAC2 as therapeutic targets in sickle cell disease, *Proc. Natl. Acad. Sci. USA*, 107(28):12617–12622, 2010 DOI: 10.1073/pnas.1006774107 (http://dx.doi.org/10.1073/pnas.1006774107)

