Researchers find new genetic target for sickle cell disease therapy

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Researchers have identified a gene that directly affects the production of a form of hemoglobin that is instrumental in modifying the severity of the inherited blood disorders sickle cell disease and thalassemia. The discovery could lead to breakthrough therapies for sickle cell disease and thalassemia, which could potentially eliminate the devastating and life-threatening complications of these diseases, such as severe pain, damage to the eyes and other organs, infections, and stroke.

"Human Fetal Hemoglobin Expression is Regulated by the Developmental Stage-Specific Repressor BCL11A," is published online in *Science* December 4. The study was conducted by researchers at Children's Hospital Boston and Dana-Farber Cancer Institute and supported by the National Institutes of Health's National Heart, Lung, and Blood Institute (NHLBI) and National Institutes of Diabetes and Digestive and Kidney Diseases, and by the Howard Hughes Medical Institute.

Hemoglobin is the protein in red blood cells that carries oxygen to the body's tissues. In sickle cell disease, hemoglobin is abnormal and sticks together. The red blood cells become stiff and sickle-shaped, causing them to block blood vessels and rob tissues of necessary blood and oxygen. In thalassemia, the body has trouble producing adult forms of hemoglobin.

Other studies have shown that in patients with sickle cell disease, those who continue to produce fetal hemoglobin (HbF) have much milder forms of sickle cell anemia. For years, scientists have sought ways to increase HbF production in patients with sickle cell disease and thalassemia.

Researchers report that by suppressing a gene called BCL11A, HbF production improves dramatically. Their findings provide new insights into the mechanisms involved in the body's switch from producing fetal hemoglobin to adult hemoglobin and identify a potential new target for therapies that could dramatically alter the course of sickle cell anemia and thalassemia.

The researchers built upon their recently reported results of genome-wide association studies that identified several gene variants associated with HbF levels. BCL11A was found to have the greatest effect on HbF levels. In the follow-up study reported today, they report that BCL11A encodes a transcription factor that directly suppresses HbF production.

A drug therapy that increases HbF levels enough to modify the severity of sickle cell disease is currently available. The drug hydroxyurea was approved by the FDA in 1998 to prevent pain crises in adults with sickle cell disease after studies showed that it increases fetal hemoglobin production, reduces the damaging effects of sickle cell disease, and improves some aspects of quality of life. Use of hydroxyurea is limited, however, in part because not all patients respond to the drug, and there are short-term and long-term adverse effects. New therapies targeting BCL11A would be the first to directly affect the natural processes involved in increasing HbF.

Sickle cell disease is the most common inherited blood disorder. In the United States, it affects approximately 70,000 people, primarily African Americans. Worldwide, sickle cell anemia affects millions of people and is found in people whose families come from Africa, South or Central America (especially Panama), Caribbean islands, Mediterranean countries, India, and Saudi Arabia. The pain and complications associated with sickle cell disease can have a profound impact on patients' quality of life, ability to work, and long-term health and well-being. In addition, people with sickle cell disease have a shortened life expectancy due to infections, lung problems, and stroke. Treatments developed over the past three decades have led to the doubling of the life expectancy of sickle cell disease patients between 1972 and

2002. These treatments include medications, blood and bone marrow transfusions, and other procedures to relieve or prevent complications. Until now, however, scientists could not directly target processes known to affect the severity of sickle cell disease.

Source: National Heart, Lung and Blood Institute