New approach to sickle-cell disease shows promise in mice

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A new genetic approach to treating sickle cell disease is showing promising results in mice, report researchers from Children's Hospital Boston. By inactivating a gene they previously discovered to be important in the laboratory, they were able to boost production of a healthy fetal form of hemoglobin in the mice, potentially compensating for the defective adult hemoglobin that causes red blood cells to "sickle" and obstruct blood flow.

The study was presented by first author Jian Xu, PhD, on Sunday, December 6, at the American Society for Hematology meeting in New Orleans.

Currently, there are only a limited number of therapies available for patients with sickle cell disease, the most common inherited blood disorder in the U.S., says senior study author Stuart H. Orkin, MD, of Children's Division of Hematology/Oncology, also David G. Nathan Professor of Pediatrics at Harvard Medical School.

Shortly after birth, babies switch from producing the fetal form of hemoglobin, the protein inside red blood cells that carries oxygen, to producing the adult form - the type that is affected in sickle cell disease. It's long been known that people who retain the ability to produce fetal hemoglobin have much milder disease. In previous studies, the Children's researchers, with collaborators, found that a gene called BCL11A is involved in switching off fetal hemoglobin production in adults. Working with genetically engineered mice, they then explored whether that switch could be turned back on to alleviate the disease.

In embryonic mice, inactivation of the BCL11A gene led to a robust expression of gamma-globin (the long protein chains making up the fetal form of hemoglobin) during late gestation: more than 90 percent of the globin produced was of this fetal type. In adult mice (8-10 weeks old), inactivation of the BCL11A gene in the blood system resulted in more than a 1,000-fold increase in gamma-globin production in bone marrow erythroblasts (the precursors to red blood cells) as compared with control mice. This increase was rapid and persisted during the course of the experiments (up until the mice were 25 weeks old).

This line of research began with comprehensive gene association studies, published in 2008 with collaborators at the Broad Institute of Harvard and MIT. These studies, involving 1600 patients with sickle cell disease, identified five DNA sequence variants (altered strings of genetic code) that correlated with fetal hemoglobin levels. BCL11A, on chromosome 2, had the largest effect, and Orkin and Vijay Sankaran, an MD-PhD student working with Orkin, later demonstrated that this gene directly suppresses fetal hemoglobin production.

If these preliminary results in mice hold up in human studies, inactivating BCL11A may also help patients with thalassemia, another blood disorder involving abnormal hemoglobin, adds Orkin.

Source: Children's Hospital Boston (news : web)