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Correcting sickle cell disease with stem cells

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(Medical Xpress) -- Using a patient's own stem cells, researchers at Johns Hopkins have corrected the genetic alteration that causes sickle cell disease (SCD), a painful, disabling inherited blood disorder that affects mostly African-Americans. The corrected stem cells were coaxed into immature red blood cells in a test tube that then turned on a normal version of the gene.

The research team cautions that the work, done only in the laboratory, is years away from clinical use in patients, but should provide tools for developing gene therapies for SCD and a variety of other blood disorders.

In an article published online August 31 in Blood, the researchers say they are one step closer to developing a feasible cure or long-term treatment option for patients with SCD, which is caused by a single DNA letter change in the gene for adult hemoglobin, the principle protein in red blood cells needed to carry oxygen. People who inherited two copies — one from each parent — of the genetic alteration, the red blood cells are sickle-shaped, rather than round. The misshapen red blood cells clog blood vessels, leading to pain, fatigue, infections, organ damage and premature death.

Although there are drugs and painkillers that control SCD symptoms, the only known cure — achieved rarely — has been bone marrow transplant. But because the vast majority of SCD patients are African-American and few African-Americans have registered in the bone marrow registry, it has been difficult to find compatible donors, says Linzhao Cheng,

Ph.D., a professor of medicine and associate director for basic research in the Division of Hematology and also a member of the Johns Hopkins Institute for Cell Engineering. “We’re now one step closer to developing a combination cell and gene therapy method that will allow us to use patients’ own cells to treat them.”

Using one adult patient at The Johns Hopkins Hospital as their first case, the researchers first isolated the patient’s bone marrow cells. After generating induced pluripotent stem (iPS) cells — adult cells that have been reprogrammed to behave like embryonic stem cells — from the bone marrow cells, they put one normal copy of the hemoglobin gene in place of the defective one using genetic engineering techniques.

The researchers sequenced the DNA from 300 different samples of iPS cells to identify those that contained correct copies of the hemoglobin gene and found four. Three of these iPS cell lines didn’t pass muster in subsequent tests.

“The beauty of iPS cells is that we can grow a lot of them and then coax them into becoming cells of any kind, including red blood cells,” Cheng said.

In their process, his team converted the corrected iPS cells into immature red blood cells by giving them growth factors. Further testing showed that the normal hemoglobin gene was turned on properly in these cells, although at less than half of normal levels. “We think these immature red blood cells still behave like embryonic cells and as a result are unable to turn on high enough levels of the adult hemoglobin gene,” explains Cheng. “We next have to learn how to properly convert these cells into mature red blood cells.”

Only one drug treatment has been approved by the FDA for treatment of SCD, hydroxyurea, whose use was pioneered by George Dover, M.D.,

the chief of pediatrics at the Johns Hopkins Children's Center. Outside of bone marrow transplants, frequent blood transfusions and narcotics can control acute episodes.

Provided by Johns Hopkins University