Gene therapy corrects sickle cell disease in laboratory study

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Using a harmless virus to insert a corrective gene into mouse blood cells, scientists at St. Jude Children's Research Hospital have alleviated sickle cell disease pathology. In their studies, the researchers found that the treated mice showed essentially no difference from normal mice. Although the scientists caution that applying the gene therapy to humans presents significant technical obstacles, they believe that the new therapy will become an important treatment for the disease.

Sickle cell disease, which affects millions of people worldwide, arises because of a tiny genetic defect in the gene for beta-globin, a protein component of hemoglobin. This defect causes hemoglobin-containing red blood cells to tend to deform, clump and break apart. The resulting clogged blood vessels can lead to cognitive dysfunction by causing small strokes in the brain and cause damage to kidneys, liver, spleen and lungs. The only permanent cure for the disease is a bone marrow transplant to give recipients blood-forming cells that will form normal beta-globin. However, such transplants are rare because of the lack of compatible donors.

Researchers have long known that symptoms of the disease could be alleviated by persistence in the blood of an immature fetal form of hemoglobin in red blood cells. This immature hemoglobin, which usually disappears after birth, does not contain beta-globin, but another form called gamma-globin. St. Jude researchers had found that treating patients with the drug hydroxyurea encourages the formation of fetal hemoglobin and alleviates disease symptoms.

"While this is a very useful treatment for the disease, our studies indicated that it might be possible to cure the disorder if we could use gene transfer to permanently increase fetal hemoglobin levels," said Derek Persons, M.D., Ph.D., assistant member in the St. Jude Department of Hematology.

He and his colleagues developed a technique to insert the gene for gamma-globin into blood-forming cells using a harmless viral carrier. The researchers extracted the blood-forming cells, performed the viral gene insertion in a culture dish and then re-introduced the altered blood-forming cells into the body. The hope was that those cells would permanently generate red blood cells containing fetal hemoglobin, alleviating the disease.

In the experiments, reported in the advanced, online issue of the journal *Molecular Therapy*, the researchers used a strain of mouse with basically the same genetic defect and symptoms as humans with sickle cell disease. The scientists introduced the gene for gamma-globin into the mice's blood-forming cells and then introduced those altered cells into the mice.

The investigators found that months after they introduced the altered blood-forming cells, the mice continued to produce gamma-globin in their red blood cells.

"When we examined the treated mice, we could detect little, if any, disease using our methods," said Persons, the paper's senior author. "The mice showed no anemia, and their organ function was essentially normal."

The researchers also transplanted the altered blood-forming cells from the original treated mice into a second generation of sickle cell mice to show that the gamma-globin gene had incorporated itself permanently

into the blood-forming cells. Five months after that transplantation, the second generation of mice also showed production of fetal hemoglobin and correction of their disease.

"We are very encouraged by our results," Persons said. "They demonstrate for the first time that it is possible to correct sickle cell disease with genetic therapy to produce fetal hemoglobin. We think that increased fetal hemoglobin expression in patients will be well tolerated and the immune system would not reject the hemoglobin, in comparison to other approaches."

While Persons believes that the mouse experiments will lead to treatments in humans, he cautioned that technical barriers still need to be overcome. "It is far easier to achieve high levels of gene insertion into mouse cells than into human cells," he said. "In our mouse experiments, we routinely saw one or two copies of the gamma-globin gene inserted into each cell. However, in humans this insertion rate is at least a hundred-fold less."

Persons' laboratory is currently working with other animal and human cells to develop methods to achieve a high enough gene insertion rate to make the gene therapy clinically useful.

Source: St. Jude Children's Research Hospital

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