Scientists successfully reprogram blood cells

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Researchers have transplanted genetically modified hematopoietic stem cells into mice so that their developing red blood cells produce a critical lysosomal enzyme -preventing or reducing organ and central nervous system damage from the often-fatal genetic disorder Hurler's syndrome.

The research team from Cincinnati Children's Hospital Medical Center reports its preclinical laboratory results this week in the early edition of Proceedings of the National Academy of Sciences.

The study suggests a new approach to molecular gene therapy and a much-needed improved treatment option for children with Hurler's syndrome, said Dao Pan, Ph.D., a researcher in the Division of Experimental Hematology/Cancer Biology at Cincinnati Children's and the study's principal author. It also is the first study to demonstrate that developing red blood cells can be used to produce lysosomal enzymes.

"The idea behind this is gene insertion so that after one treatment a person would be cured," said Dr. Pan. "In the mouse models receiving this treatment, the pathology of the peripheral organs tested was completely normalized. And although not as complete, we also saw significantly improved neurological function and brain pathology."

Hurler's syndrome is the severe form of MPS type1, or mucopolysaccharidoses. MPS type1 and similar genetic disorders are known as lysosomal storage disease, which are caused by the body's inability to produce specific lysosomal enzymes. Lysosomes, part of a cell's internal machinery, help the body's cells break down large

molecules and recycle materials to fuel the healthy development and maintenance of vital organ and nerve tissues.

The lysosomes in the cells of children with Hurler syndrome do not have a vital enzyme called IDUA (/a-/L-idunronidase). This causes their cells to accumulate too much of a class of biochemical known as mucopolysaccharides, in this instance dermatan sulfate and heparin sulfate. This excess accumulation results in progressive tissue damage to organs and the central nervous system and typically results in early death.

Dr. Pan and her colleagues initially experimented on the cells of patients with Hurler syndrome that were cultured in the laboratory. They successfully used what is called a viral vector (in this case a lentivirus) to insert a healthy version of the IDUA gene into early stage red blood cell cultures, and a hybrid promoter gene, to prompt the cells to produce the IDUA enzyme. This could allow the enzyme to be absorbed by a patient's other cells to correct functional defects in the lysosomes.

Encouraged by the initial cell experiments, the research team next cultured hematopoietic stem cells taken from mouse models of MPS I. They did so using the same hybrid promoter gene from the earlier experiments to reprogram the stem cells to produce IDUA. They then performed bone marrow transplantation on the MPS I mice with the reprogrammed cells. The developing red blood cells in these mice produced large amounts of IDUA in the blood stream, which was absorbed by other cells that help make tissues for vital organs and the central nervous system.

Of particular interest to Dr. Pan and her colleagues was the ability of the IDUA in circulating blood to somehow bypass the blood brain barrier - normally a severe limitation in treating diseases that affect the central nervous system.

Besides Hurler syndrome, Dr. Pan said the study will have positive implications in the treatment of many other lysosomal storage diseases, which affect different parts of the body, depending on the specific enzyme deficiency. She also said this particular approach to gene therapy carries considerably less risk of stimulating cancer genes, which has been a concern with some forms of gene therapy. This is because the researchers used a promoter gene specific to red cells to stimulate IDUA production, and they did so in just one specific subset of blood cells (and not in any other offspring from genetically modified blood stem cells).

One current treatment method for Hurler syndrome includes bone marrow transplant from a healthy matched donor. These treatments have a mortality rate of 20 to 30 percent if patients can find a matched donor. Dr. Pan said reprogramming a patient's own developing red blood cells by gene therapy would provide a viable option for patients who cannot find a donor and avoid potential complications caused by an immune response to donor cells.

Another current treatment option is a pharmaceutical version of IDUA, although the therapy is limited because it cannot cross the blood brain barrier to address problems in the central nervous system. It also requires repeated life-long treatment.

Dr. Pan said additional research is needed to further verify the viral vectors used by the researchers, to evaluate the efficacy of this approach in larger animal models and to explain the molecular reasons for its success, especially the ability to cross the blood-brain barrier.

Source: Cincinnati Children's Hospital Medical Center (news : web)