Gene Therapy-Possible treatment for Sickle Cell

In this article, Genetic Engineering& Biotechnology News highlights the use of technology to provide a possible new treatment for sickle cell anemia. In the experiment, scientist from Cornell use technology “based on delivery of a lentiviral vector carrying both the human β-globin gene and an ankyrin insulator to improve gene transcripton and translation, and boost levels of β-globin production.” (Gene Therapy Shows Promise for Treating Beta- Thalassemia and Sickle Cell Disease) The results of this technology created and increased level of hemoglobin and oxygen in lab mice.

The effects of this treatment on sickle cell patients, if proven successful, would be tremendous. Many symptoms would be less severe, including anemia due to the elevated oxygen levels. There would be a decrease in the need for blood transfusions which would strengthen their veins and allow them to recover from being poked and prodded. Negative effects of this treatment may be the price, which would discourage most patients from using this medicine. This experiment could be ground breaking news in the world of genetic engineering and science, however many things have to be worked out before it is available to humans.

Treatment with Gene Therapy

Scientists have developed a gene therapy strategy that could feasibly treat both β-thalassemia and sickle cell disease. The technology is based on delivery of a lentiviral vector carrying both the human β-globin gene and an ankyrin insulator to improve gene transcripton and translation, and boost levels of β-globin production. The Weill Cornell Medical College-led team that reports on the development has in parallel devised a simple assay to predict how well individual patients are likely to respond to the treatment.

Stefano Rivella, Ph.D., and colleagues report on their achievement in PLoS One in a paper titled “Therapeutic Hemoglobin Levels after Gene Transfer in β-Thalassemia Mice and in Hematopoietic Cells of β-Thalassemia and Sickle Cells Disease Patients.”

β-thalassemia is caused by mutations in the β-globin gene which lead to either reduced β-globin synthesis (β+), or a complete lack of β-globin (β0). Sickle-cell disease (SCD), on the other hand, is caused by a mutation in the β chain that leads to synthesis of an aberrant form of hemoglobin, Hb S. The only definitive cure for either disease is allogeneic bone marrow cell transplantation, a procedure that, even if a suitable donor can be found, can cause rejection reactions in the recipient.

Building on the success of prior gene therapy studies in mice, and the first evaluation of gene therapy in β-thalassemia patient, the Weill Cornell-led researchers developed a new lentiviral vector, designated AnkT9W, which carries both the human β-globin gene and the erythroid-specific ankyrin 5’ hypersensitive (HS) barrier insulator.

Initial studies showed that mouse erythroleukemia (MEL) cells transduced with AnkT9W exhibited far greater hemoglobin synthesis than cells transduced with a T9W vector that didn’t include the ankyrin insulator. This enhanced hemoglobin synthesis was associated with increased levels of β-globin mRNA and translation. Importantly, the ankyrin element was stably integrated in the MEL cells.

The researchers moved on to test their vector in a mouse model of thalassemia intermedia, which is the less severe form of the disease. Bone marrow cells from affected mice were transduced with AnkT9W and then reintroduced back into the animals. Encouragingly, therapy led to markedly increased levels of hemoglobin and red cell counts, together with what the authors call remarkable correction of the red blood cell morphology, and correction of liver and spleen morphology.

To demonstrate whether expression of chimeric hemoglobin could be sustained over the long term, the team then took bone marrow cells from the treated animals and transplanted them into a separate cohort of thalassemic mice, and then repeated the process to establish tertiary chimeras. Even in these animals expression of chimeric hemoglobin was comparable to that of the initial treated animals, “confirming that a sustained correction of the phenotype can be achieved utilizing AnkT9W.”

Given that the data so far indicated that AnkT9W enabled MEL cells to express the transgenic β-globin gene and led to efficient long-term correction of thalassemic phenotype in mice, the team tested the vector in an ex vivo-expanded population of peripheral blood-derived human erythroid progenitor cells (ErPCs). Transduced cells from patients with β+ thalassemia (i.e., that already produce some Hb A) started to produce levels of total Hb A (in other words transgenic Hb A plus endogenous Hb A) that were equivalent to those in healthy cells. Even totally Hb A-deficient β0 cells were capable of producing levels of transgenic Hb A comparable to about 55% of normal, after transduction with AnkT9W.

Overall, it was evident that β0/0 cells required higher amounts of vector to reach therapeutic levels of Hb, whereas Β0/+ and β+/+ cells already expressed some endogenous HbA and reached curative levels at lower vector copy numbers (VCNs). Blood tests prior to therapy could therefore provide an indication of how much vector they will need to achieve curative levels of Hb, the team writes. “We believe that analysis of erythroid progenitors transduced with different amounts of lentiviral vectors could be useful for testing the potential of each lentiviral construct prior to bone marrow transplantation.”

Results in CD34+ cells from SCD patients were similarly encouraging. These cells normally produce no Hb A, but instead produce a mutant Hb S. However, after transduction with AnkT9W, the cells reduced their production of both fetal hemoglobin and Hb S, and instead started producing transgenic Hb A.

"This study represents a fresh departure from previously published work in the field of gene therapy,” Dr. Rivella claims. “The gene therapy technique has the potential to cure many patients, especially if we prescreen them to predict their response using just a few of their cells...This approach would provide vital information to select the best candidates for these clinical trials, before patients undergo myeloablation and bone marrow transplant.”

“Gene Therapy Shows Promise for Treating Beta- Thalassemia and Sickle Cell Disease.” Genetic Engineering and Biotechnology News. March 28, 2012. <http://www.genengnews.com/gen-news-highlights/gene-therapy-shows-promise-for-treating-beta-thalassemia-and-sickle-cell-disease/81246554/>. 29 Mar 2012