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# Embryonic stem cells help deliver 'good genes' in a model of inherited blood disorder

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Researchers at Nationwide Children's Hospital report a gene therapy strategy that improves the condition of a mouse model of an inherited blood disorder, Beta Thalassemia. The gene correction involves using unfertilized eggs from afflicted mice to produce a batch of embryonic stem cell lines. Some of these stem cell lines do not inherit the disease gene and can thus be used for transplantation-based treatments of the same mice. Findings could hold promise for a new treatment strategy for autosomal dominant diseases like certain forms of Beta Thalassemia, tuberous sclerosis or Huntington's disease.

Embryonic stem cells have the potential to produce unlimited quantities of any cell type and are therefore being explored as a new therapeutic option for many diseases. Unfertilized eggs can be cultured to form embryonic stem cells, so-called parthenogenetic embryonic stem cells.

"Parthenogenetic embryonic stem cells can differentiate into multiple tissue types as do stem cells from fertilized embryos," said K. John McLaughlin, PhD, principal investigator in the Center for Molecular and Human Genetics at The Research Institute at Nationwide Children's Hospital. Previously, the group demonstrated that blood cells derived from parthenogenetic cells could provide healthy, long-term blood replacement in mice.

"Advantages of parthenogenetic stem cells are not only that fertilization is not needed, but also that the recipient's immune system may potentially not view them as foreign, minimizing rejection problems.

Furthermore, since parthenogenetic embryonic stem cells are derived from reproductive cells which contain only a single set of the genetic information instead of the double set present in body cells, they may not contain certain abnormal genes present in the other copy," said Dr. McLaughlin also one of the study authors.

A single copy of an abnormal gene inherited from one parent can cause so-called autosomal dominant diseases such as tuberous sclerosis or Huntington's disease. The affected person has one defective and one normal copy of the gene, but the abnormal gene overrides the normal gene, causing disease. In normal sexual reproduction, each parent provides one gene copy to offspring via their reproductive cells. Therefore, the reproductive cells of a patient with an autosomal dominant disease could either pass along a defective copy or a normal copy.

"As the donor patient has one defective gene copy and one normal, and only one copy is used for normal reproduction, we can select egg-cell-derived embryonic stem cells with two normal copies," said Dr. McLaughlin. "These single-parent/patient-derived embryonic stem cells can theoretically be used for correction of a diverse number of diseases that occur when one copy of the gene is abnormal," said Dr. McLaughlin.

To test this theory, Dr. McLaughlin and colleagues from the University of Pennsylvania, University of North Carolina and University of Minnesota, examined whether parthenogenetic embryonic stem cells could be used for tissue repair in a mouse model of thalassemia intermedia. Thalassemia intermedia is an inherited blood disorder in which the body lacks sufficient normal hemoglobin, leading to excessive destruction of red blood cells and anemia. They used a mouse model in which one defective gene copy causes anemia.

Using approaches developed from a previous study done by this group, Nationwide Children's Research Fellow Sigrid Eckardt, PhD, derived embryonic stem cells from the unfertilized eggs of female mice with the disease, and identified those stem cell lines that contained only the "healthy" hemoglobin genes. These "genetically clean" embryonic stem cell lines were converted into cells that were transplanted into afflicted mice that were carriers of the disease causing gene. Blood samples drawn five weeks after transplantation revealed that the delivered cells were present in the recipients' blood. Their red blood cells were also corrected to a size similar to normal mice and red blood cell count, hematocrit and hemoglobin levels became normal.

"Overall, we observed long-term improvement of thalassemia in this model," said Dr. Eckardt. "Our findings suggest that using reproductive cells to generate embryonic stem cells that are 'disease-free' may be a solution for genetic diseases involving large, complex or poorly identified deletions in the genome or that are not treatable by current gene therapy approaches." Dr. McLaughlin says that this approach also contrasts with typical gene therapy approaches in that it requires no engineering of the genome, which is currently difficult to achieve in human embryonic and embryonic-like (IPS) stem cells.

Provided by Nationwide Children's Hospital

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