Stem cells restore sight in mouse model of retinitis pigmentosa

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An international research team led by Columbia University Medical Center successfully used mouse embryonic stem cells to replace diseased retinal cells and restore sight in a mouse model of retinitis pigmentosa. This strategy could potentially become a new treatment for retinitis pigmentosa, a leading cause of blindness that affects approximately one in 3,000 to 4,000 people, or 1.5 million people worldwide. The study appears online ahead of print in the journal *Transplantation* (March 27, 2010 print issue).

Specialized retinal cells called the retinal pigment epithelium maintain vision. Retinitis pigmentosa results from the death of retinal cells on the periphery of the retina, leading to "tunnel vision," where the field of vision is narrowed considerably and everything outside the "tunnel" appears blurred or wavy.

"This research is promising because we successfully turned stem cells into retinal cells, and these retinal cells restored vision in a mouse model of retinitis pigmentosa," said Stephen Tsang, M.D., Ph.D., assistant professor of ophthalmology, pathology and cell biology, Columbia University Medical Center, and lead author of the paper. "The transplanted cells not only looked like retinal cells, but they functioned like them, too."

In Dr. Tsang's study, sight was restored in one-fourth of the mice that received the stem cells. However, complications of benign tumors and retinal detachments were seen in some of the mice, so Dr. Tsang and

colleagues will optimize techniques to decrease the incidence of these complications in human embryonic stem cells before testing in human patients can begin.

"Once the complication issues are addressed, we believe this technique could become a new therapeutic approach for not only retinitis pigmentosa, but age-related macular degeneration, Stargardt disease, and other forms of retinal disease that also feature loss of retinal cells," said Dr. Tsang.

In age-related macular degeneration, retinal cells in the center of the retina degenerate and cause the center part of vision to become blurry or wavy. In 2010, macular degeneration is prevalent in nine million Americans and its incidence is expected to double by 2020. It is estimated that 30 percent of the population will have some form of macular degeneration by the time they reach the age of 75.

Replacement of damaged retinal cells in patients with macular degeneration is currently offered in some hospitals, but the therapy is limited by a shortage of donor retinal pigment epithelium cells. By using stem cells and turning them into retinal pigment epithelium cells, the supply is virtually unlimited.

Similar approaches to macular degeneration have demonstrated efficacy in other rodent models, but since these models are of rare, unique pathophysiologies of retinal degeneration, they may not be generalizable to most human forms of retinal degeneration, e.g., age-related macular degeneration, retinitis pigmentosa or Stargardt disease.

"It's a good thing that more models are being tried, as this shows there may be real potential for stem cells to treat different causes of the loss of retinal pigment epithelium in humans," said Dr. Tsang.

Research Used Highly Technical Methods Developed at Columbia

The research methods used in this study were developed by Columbia researchers, past and present, including:

- Dr. Peter Gouras (ophthalmology) pioneered retinal cell transplantation where stem cells are placed underneath the retina. Co-authors on this paper, Drs. Nan-Kai Wang (a former retinal fellow now at the Chang Gung Memorial Hospital, the Chang Gung University College of Medicine and National Taiwan University in Taiwan) and Joaquin Tosi (ophthalmology) used this technique to place transplanted stem cells underneath the retina.

- Dr. Gouras also developed many of the non-invasive methods used to assess neuronal function in mouse visual system, such as electroretinography, which measures the retina's response to light.

- The strategies for embryonic stem cell use were developed at Columbia by Dr. Elizabeth J. Robertson (now at Oxford). In collaboration with Dr. Pamela L. Schwartzberg (now at the National Institutes of Health), and Dr. Stephen P. Goff (biochemistry, molecular biophysics and microbiology), Dr. Robertson combined embryonic stem cells with homologous recombination to achieve gene targeting, producing the first gene-targeted mice.

- The techniques employed to engineer stem cells were developed at Columbia by Drs. Goff and Virginia E. Papaioannou

(genetics).

- Co-author Dr. Victor Chyuan-Sheng Lin (pathology) tapped Dr. Martin Chalfie's (biological sciences) Nobel Prize winning work on green fluorescent protein, to turn the stem cells used in this research yellow, enabling the team to use imaging to see them non-invasively in the mice.

- Dr. Takayuki Nagasaki (ophthalmology) developed an advanced imaging technique, known as fundus autofluorescence imaging, which enabled the researchers to examine the mouse eye using non-invasive methods.

"I am fortunate that this diverse expertise exists at the same university - Columbia is one of the few places in the world where this research could be conducted," said Dr. Tsang. "And our multidisciplinary approach to basic science research is unique."

Provided by Columbia University Medical Center