Two novel treatments for retinitis pigmentosa move closer to clinical trials

December 20 2012

Two recent experimental treatments—one involving skin-derived induced pluripotent stem (iPS) cell grafts, the other gene therapy—have been shown to produce long-term improvement in visual function in mouse models of retinitis pigmentosa (RP), according to the Columbia University Medical Center (CUMC) scientists who led the studies. At present, there is no cure for RP, the most common form of inherited blindness.

"While these therapies still need to be refined, the results are highly encouraging," said Stephen H. Tsang, MD, PhD, associate professor of pathology & cell biology and of ophthalmology at Columbia University Medical Center and an ophthalmologist at NewYork-Presbyterian Hospital/CUMC, the leader of both studies. "We've never seen this type of improvement in retinal function in mouse models of RP. We hope we may finally have something to offer patients with this form of vision loss."

The stem cell study was published in the journal *Molecular Medicine*. The gene therapy study was published in Human Molecular Genetics.

RP encompasses a group of inherited eye diseases that cause progressive loss of photoreceptor cells, specialized neurons found in the retina. While RP can appear during infancy, the first symptoms typically appear in early adulthood, beginning with night blindness. As the disease progresses, affected individuals lose peripheral vision. In later stages, RP destroys photoreceptors in the macula, which is responsible for fine

central vision. Mutations in at least 50 genes have been found to cause the disease, which affects about 1.5 million people worldwide.

In the *Molecular Medicine* study, the CUMC researchers tested the long-term safety and efficacy of using iPS cell grafts to restore visual function in a mouse model of RP. Like embryonic stem cells, iPS cells are "pluripotent"—that is, they are capable of developing into any cell type. However, iPS cells are not derived from embryos but from adult cells, in this case from human skin cells. The cells were administered, via injection directly underneath the retina, when the mice were five days old.

The iPS cells assimilated into the host retina without disruption, and none of the mice receiving transplants developed tumors over their lifetimes, the researchers reported. The iPS cells were found to express markers specific to retinal pigmented epithelium (the cell layer adjacent to the photoreceptor layer), showing that they had the potential to develop into functional retinal cells. Using electroretinography, a standard method for measuring retinal function, the researchers found that the visual function of the mice improved after treatment and the effect was long lasting. "This is the first evidence of lifelong neuronal recovery in an animal model using stem cell transplants, with vision improvement persisting throughout the lifespan," said Dr. Tsang.

In 2011, the FDA approved clinical trials of embryonic stem cell transplants for the treatment of macular degenerations, but such therapy requires immunosuppression. "Our study focused on patient-specific iPS cells, which offer a compelling alternative," said Dr. Tsang. "The iPS cells can provide a potentially unlimited supply of cells for functional rescue and optimization. Also, since they would come from the patient's own body, immunosuppression would not be necessary to prevent rejection after transplantation."

In theory, iPS cell transplants could also be used to treat age-related macular degeneration, the leading cause of vision loss among older adults, said Dr. Tsang.

In the Human Molecular Genetics study, the CUMC researchers tested whether gene therapy could be used to improve photoreceptor survival and neuronal function in mice with RP caused by a mutation to a gene called phosphodiesterase-alpha (Pde6α)—a common form of the disease in humans. To treat the mice, the researchers used adeno-associated viruses (AAV) to ferry correct copies of the gene into the retina. The AAV were administered by a single injection in one eye, with the other eye serving as a control.

When the mice were examined at six months of age (over one-third of the mouse lifespan), photoreceptor cells were found in the treated eyes but not in the untreated eyes, the researchers reported. More important, the treated eyes showed functional visual responses, while the untreated eyes had lost all vision.

"These results provide support that RP due to PDE6α deficiency in humans is also likely to be treatable by gene therapy," said Dr. Tsang.

More information: The *Molecular Medicine* paper is titled, "Stem Cell (iPS) Grafts in a Preclinical Model of Retinitis Pigmentosa."

Provided by Columbia University Medical Center