Gene therapy restores vision to mice with retinal degeneration

October 16 2008

Massachusetts General Hospital (MGH) researchers have used gene therapy to restore useful vision to mice with degeneration of the light-sensing retinal rods and cones, a common cause of human blindness. Their report, appearing in the Oct. 14 *Proceedings of the National Academy of Sciences,* describes the effects of broadly expressing a light-sensitive protein in other neuronal cells found throughout the retina.

"This is a proof of principle that someday we may be able to repair blindness in people with conditions like retinitis pigmentosa and macular degeneration," says Richard Masland, PhD, director of the Cellular Neurobiology Laboratory in the MGH Department of Neurosurgery. "There are several limitations we need to overcome before we can begin clinical trials, but I'm optimistic that this work may someday make a big difference for people who otherwise would have no vision at all."

The study was designed to investigate the effect of expressing the light-sensitive protein melanopsin in retinal ganglion cells. These specialized neurons receive light signals from the rods and cones and carry those signals into the brain via the optic nerve, which is formed from the cells' axons. Melanopsin is usually produced in a subset of cells that are involved with establishing circadian rhythms but not with vision. The MGH team used the standard viral vector adeno-associated virus to deliver the gene encoding melanopsin throughout the retinas of mice whose rod and cone photoreceptors had degenerated from lack of a crucial protein.

Four weeks after delivery of the gene, melanopsin – normally produced in 1 percent of retinal ganglion cells – was found in about 10 percent of ganglion cells in the treated eyes but not in eyes that received a sham injection. Many of the melanopsin-expressing cells were structurally different from those that typically produce the protein, implying that it was being expressed in a broader range of retinal ganglion cells. Electrophysiological examination of the melanopsin-expressing cells revealed that all responded to light, although the neuronal signal was delayed and persisted after the light signal had stopped, which is typical for a melanopsin-mediated signal. Two behavioral tests verified that the treated mice – which otherwise would have been essentially blind – had enough vision to find a darkened refuge in an otherwise brightly-lit area and to successfully learn that a light indicated a safe platform to which they could swim.

"The same level of melanopsin expression in a human retina might allow someone who otherwise would be totally blind to read newspaper headlines, but the slowness of the response would be a problem," Masland says. He notes that another group's gene therapy experiments published earlier this year were similar but used a protein that requires a level of light comparable to looking directly into a bright sky for a whole day, which would eventually damage the retina. "Before planning clinical trials, we need to develop a more sensitive version of the other protein, channelrhodopsin-2, or a faster-responding melanopsin, which we are working on."

Source: Massachusetts General Hospital