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Research Identifies Promising Route for Treating Age-Related Hearing Loss



Image Title: An old family photograph from the collection of HHMI investigator David P. Corey demonstrates one method that was used to compensate for age-related hearing loss. In the photograph, which was taken around 1910, the young girl, who is Corey's grandmother, uses a speaking tube to communicate with Corey's great-great-grandfather. - Courtesy of David P. Corey

Researchers have discovered that deletion of a specific gene permits the proliferation of new hair cells in the cochlea of the inner ear—a finding that offers promise for treatment of age-related hearing loss. This type of hearing loss is caused by aging, disease, certain drugs, and the cacophony of modern life. It is the most common cause of hearing loss in older people.

The research team, which included Howard Hughes Medical Institute investigator David P. Corey, published their findings on January 13, 2005, in *Science Express*, which provides rapid electronic publication of selected *Science* publications. Zheng-Yi Chen, who is at Massachusetts General Hospital and Harvard Medical School, is the senior author of the article. He trained with Corey at Harvard Medical School. Other co-authors are from the University of Virginia School of Medicine, Tufts-New England Medical Center, and Northwestern University.

Hair cells in the cochlea detect sound by vibrating in response to sound waves, triggering nerve impulses that travel to the auditory region of the brain. Normally, humans are born with a complement of about 50,000 hair cells. But since the cells do not regenerate, the steady rate of hair-cell loss that can accompany aging produces significant hearing loss in about a third of the population by the time they reach 70-years-old.

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Chen did a broad survey that examined patterns of gene expression during embryonic development of the balance organ of the inner ear. His results suggested that there might be a gene that produces a protein that acts as a permanent "brake" on hair-cell regeneration. That survey, which was done in mice, revealed that the retinoblastoma gene seemed to be particularly active during embryonic development.

At the same time, co-author Philip Hinds at Tufts-New England Medical Center had developed a knockout mouse lacking the retinoblastoma gene *Rb1*.

"He noticed that these mice ran in circles, and for an inner-ear biologist, a mouse running in circles immediately tells you that there is some problem with the vestibular system of the inner ear," said Corey. Thus, he said, Chen began a detailed study of the hair cells of the knockout mice. Those studies revealed that the mice without *Rb1* had more hair cells than normal mice, and the cells were actively proliferating.

Corey and his colleagues then launched studies to determine whether the proliferating cells were, indeed, functional hair cells. They found that mechanically stimulating the cells generated an electrical signal characteristic of hair cells. Also, Corey and his colleagues found that the cells absorbed a fluorescent dye that only moves through the membrane channels of

functional hair cells.

In further studies, Chen and his colleagues found that knocking out the *Rb1* gene in cultured mature inner ear cells from mice triggered the cells to begin proliferating.

“This experiment demonstrated that it was a direct effect of the *Rb* gene and not some indirect effect during development that controlled proliferation of hair cells,” said Corey. “So Zheng-Yi has found that deletion of this gene can allow functioning hair cells to continue to divide. They are no longer limited by whatever growth controls existed before. This work gives us an invaluable window into the control mechanism, which could lead to eventual clinical application in regenerating lost hair cells,” said Corey.

According to Corey, the findings also have important implications for basic research. “A major obstacle to hair-cell research has been that, since there are not very many hair cells in the inner ear, it has been hard to get enough material for study,” he said. “But with Zheng-Yi's work, we now have the potential for generating cultured lines of hair cells for experiments.”

“While we are very excited about the potential for hair-cell regeneration from this work, much basic research needs to be done,” emphasized Corey. “Simply inactivating the *Rb* gene allows the hair cells to keep dividing and dividing, which might produce tumors in the inner ear. So, Zheng-Yi and his colleagues will be seeking ways to inactivate the gene only long enough to allow a clinically useful amount of proliferation, before turning the gene back on.” The approach, he said, will require a greater understanding of the mechanisms controlling the *Rb* signaling pathway.