Genetic hearing loss may be reversible without gene therapy

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A large proportion of genetically caused deafness in humans may be reversible by compensating for a missing protein, based on discoveries in mice.

Emory University researchers have found that in mice, increasing the amount of the protein connexin26 in the ear's cochlea compensates for an absence of another protein, connexin30. The findings come 10 years after scientists first discovered that connexin26 mutations cause much of the deafness diagnosed at birth.

Xi (Erick) Lin, PhD, associate professor of otolaryngology and cell biology at Emory University School of Medicine, was lead author of the study, published recently in the *Proceedings of the National Academy of Sciences*.

"There are millions of deaf people affected by mutations in this one gene, connexin26," he says. "Congenital hearing loss is one of the most common human genetic birth defects, and that is why in almost all the states universal newborn hearing screening is mandated by law [including Georgia]."

In people without congenital hearing loss, connexin26 and connexin30 work together to form the cochlea's hybrid junction gaps, which facilitate intercellular communication. But when one of the proteins is missing, the hybrid junction gaps fail to work, and the cochlea's hair cells die off, leaving the body incapable of translating sounds into nerve

impulses.

Even though scientists knew connexin26 was implicated in congenital deafness, they did not know precisely why. Working with Emory colleagues and scientists from the University of Bonn in Germany, Dr. Lin developed contrasting hypotheses.

"The deafness could have two very different explanations," he says. "Either hybrid gap junctions have special biophysical properties that cannot be replaced by gap junctions built with only one type of connexin, or mutations in one of the two connexins just cut the supply for making the gap junctions in half."

By adding extra connexin26 to mice that were missing connexin30, Dr. Lin and his team proved the latter hypothesis. With the additional connexin26, hearing sensitivity was restored and the expected hair cell death never occurred. Those positive findings led Dr. Lin to conclude, "The problem is simply caused by not having enough protein remaining in the ear of these mutant mice to assemble gap junctions."

Dr. Lin and his colleagues are now working to see if connexin-related deafness can be reversed in a mouse model, or if increasing connexin30 may help when connexin26 is absent.

As the research picks up momentum, these results—and future findings—may mean big changes for how congenital deafness is approached. Up to now, says Dr. Lin, scientists working on hearing loss had placed all their bets on gene therapy. That may no longer make sense. "Gene therapy, which has very few successful cases so far, may not be necessary," explains Dr. Lin.

Instead, Dr. Lin's findings indicate that a drug to boost connexin26 may be all that is needed. "Our work predicts that a drug should be sufficient

to cure connexin30 deletion-caused deafness," he says.

More information: www.pnas.org/cgi/content/full/104/4/1337

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