MedicalXpress

Genetic modification shows promise for preventing hereditary hearing loss

November 6 2015

A mitochondrial defect is responsible for a type of human hereditary deafness that worsens over time and can lead to profound hearing loss. Using a genetically-modified mice model with a mitochondrial dysfunction that results in a similar premature hearing loss, researchers showed that precise genetic reduction of an enzyme, AMP kinase (AMPK), can rescue the hearing loss. Their results are reported in the *American Journal of Pathology*.

"Mitochondrial dysfunction causes human diseases, with an estimated occurrence of 1 in 5,000 to 10,000 live births. Mitochondrial diseases are complicated and heterogeneous, characterized by cell- and tissue-specific responses and pathology. An extreme example of tissue specificity is the A1555G mitochondrial DNA (mtDNA) mutation that causes maternally-inherited deafness," explained lead investigator Gerald S. Shadel, PhD, of the Departments of Pathology and Genetics at Yale School of Medicine.

To study this particular type of deafness, Dr. Shadel and colleagues bred transgenic mice that globally over-express the gene encoding transcription factor B1, mitochondrial (TFB1M). The Tfb1m protein (aka mtTFB1) modifies the 12S ribosomal RNA of mitochondrial ribosomes that are necessary to express mtDNA-encoded genes. These Tg-mtTFB1 mice develop hearing loss at a rate much faster than wild-type controls.

A collaborative group of investigators in the laboratories of Dr. Shadel

and Joseph Santos-Sacchi, PhD, Departments of Surgery, Cellular and Molecular Physiology, and Neurobiology, Yale School of Medicine, compared anatomical and functional differences in the hearing pathways of the Tg-mtTFB1 mice. In the cochlea multiple defects were observed, including in the spiral ganglion nerves and the stria vascularis. "We propose that the defects we observed in the stria, spiral ganglion neurons, and outer hair cells conspire to produce the observed hearing loss profile in Tg-mtTFB1 mice," noted Sharen McKay, PhD, Department of Pathology, Yale School of Medicine and Department of Psychology, University of Bridgeport, the first author of the study.

Specifically, the pathway to hearing loss in the Tg-mtTFB1 mice is initiated by mitochondrial reactive oxygen species that stimulate the enzyme AMPK, which then activates deleterious signaling events in specific parts of the inner ear. Thus, the investigators reasoned that reducing AMPK activity could prevent the hearing loss. To test this hypothesis, they bred Tg-mtTFB1 mice that had one of their AMPK genes knocked out. Between 9 and 12 months of age, the Tg-mtTFB1 group showed the expected increase in auditory brainstem response (ABR) threshold indicative of hearing loss (a higher threshold denotes reduced sensitivity to sound), while the Tg-mtTFB1 mice in which the AMPK gene was also knocked-out had ABR thresholds indistinguishable from those of controls.

"We conclude that reducing AMPK signaling has no effect on normal hearing at the ages tested but rescues or delays premature hearing loss in Tg-mtTFB1 mitochondrial deafness model mice. This opens the possibility for intervention in humans based on inhibiting AMPK, which is already a drug target for several diseases," stated Dr. Shadel. The team cautions, however, that additional work is needed before the results from this mouse model are used to inform pathology in maternally inherited deafness caused by mtDNA mutations in humans and to understand how these mice might shed light on prophylactic or therapeutic strategies.

More information: "Auditory pathology in a transgenic mtTFB1 mouse model of mitochondrial deafness," by Sharen E. McKay, Wayne Yan, Jessica Nouws, Max Thormann, Nuno Raimundo, Abdul Khan, Joseph Santos-Sacchi, Lei Song and Gerald S. Shadel. (DOI: dx.doi.org/10.1016/j.ajpath.2015.08.014). This article appears online ahead of The *American Journal of Pathology*, Volume 185, Issue 12 (December 2015)

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