Gene Editing Restores Hearing in Mice

By YAN Fusheng (Staff Reporter)

In a recent study published in *Science Translational Medicine*, a research team jointly led by Dr. YANG Hui from the Institute of Neuroscience of the Chinese Academy of Sciences, Dr. LI Huawei and Dr. SHU Yilai from Fudan University, showed that a new gene-editing technique called mxABE (mini dCas13X-based adenosine base editor) was able to fix a genetic mutation and restore hearing in mice with a specific type of inherited hearing loss. This research offers hope for treating sensorineural hearing loss (SNHL), a common condition currently without effective treatment, in humans.

In this study, the researchers used a mouse model suffering from a similar type of hearing loss found in humans caused by mutations in the *Myo6* gene. The *Myo6* gene provides instructions for making a protein called myosin VI, which plays a crucial role in the functioning of hair cells in the inner ear. Hair cells are responsible for converting sound vibrations into electrical signals that the brain can interpret as sound.

Mutations in the *Myo6* gene can interfere with the normal function of myosin VI, leading to problems concerning the development, maintenance, or function of hair cells. This can result in various types of hearing loss, including sensorineural hearing loss.

They developed an RNA base editing system, which combines base editors and guide RNA (gRNA), to fix the mutation in these mice. After testing various combinations of base editors and gRNAs, they found that the mxABE-v1 system was highly efficient and had low off-target effects.

To deliver the mxABE-v1 and gRNA to the mice, they used a harmless virus called adeno-associated virus (AAV). Injecting this into the inner ear of the mice led to significant improvements in their hearing function. The treated mice had better preservation of hair cells in their ears and showed decreased hearing thresholds, indicating improved hearing abilities.

Currently, there are no effective treatments for SNHL, but researchers are exploring drugs, stem cells, and gene therapy as potential strategies. Since about half of congenital SNHL cases are caused by genetic factors, gene therapy could be an important way to slow down the disease progression and improve symptoms.

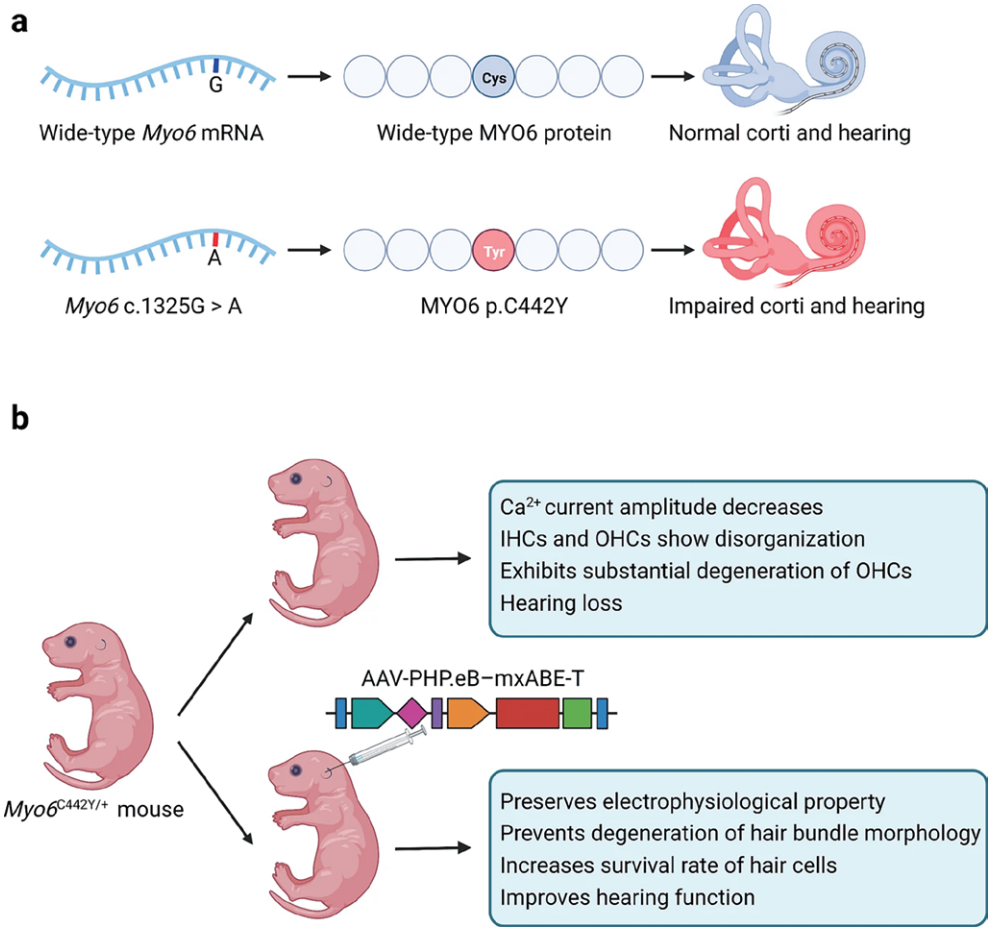
The CRISPR-Cas systems are widely used for gene editing, and base editing is a newer application that allows for precise changes in DNA or RNA. The mxABE system used in this study has several advantages, such as being reversible, non-heritable, and not requiring specific sequences for editing, making it more suitable for clinical applications.

However, there are still challenges to overcome before this technique can be used in humans. One concern is the safety of using AAVs to deliver gene therapy, as some cases have raised concerns about their potential side effects. It is crucial to find the best way to deliver the mxABE system with high efficiency, specificity, and low safety risks. Lipid nanoparticles (LNPs) have shown promise in delivering genetic material in mRNA vaccines, and they could potentially be used for this purpose as well.

Additionally, researchers need to work on improving the efficiency and accuracy of the mxABE system to minimize off-target effects. This could involve optimizing gRNA design, developing high-fidelity Cas endonucleases, and discovering new anti-CRISPR proteins or small molecule drugs that can act as safeguards.

Lastly, clear international laws and regulations are needed to address ethical concerns regarding the use of gene-editing techniques in humans.

This study demonstrates that the mxABE gene-editing



Gene-editing technique helps restore hearing in mice. a) A base mutation from G to A in the *Myo6* mRNA leads to a change of amino acid in the final protein, which fails to maintain the normal function of hair cells in the mouse's inner ear, leading to hearing loss. b) A new gene-editing technique called mxABE was able to restore or improve hearing function by proofreading and rewriting the mutation from A to G. (Credit: LIU *et al./ Signal Transduction and Targeted Therapy*)

technique can correct a specific genetic mutation and help restore hearing in mice. This research provides a promising starting point for developing RNA editing tools as potential treatments for sensorineural hearing loss and other genetic diseases.

Notably, in another study, the mxABE strategy has also been demonstrated to restore dystrophin expression in a mouse model of Duchenne muscular dystrophy. A gene transfer therapy study to evaluate the safety and efficacy of a similar mxABE-based gene transfer therapy in participants with Duchenne muscular dystrophy is currently active (Identifier: NCT05096221), according to Dr. YANG Hui from the CAS Institute of Neuroscience, who leads the study.

References

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