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Prevention of acquired sensorineural hearing loss in mice by in vivo *Htra2* gene editing

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Abstract

Background: Aging, noise, infection, and ototoxic drugs are the major causes of human acquired sensorineural hearing loss, but treatment options are limited. CRISPR/Cas9 technology has tremendous potential to become a new therapeutic modality for acquired non-inherited sensorineural hearing loss. Here, we develop CRISPR/Cas9 strategies to prevent aminoglycoside-induced deafness, a common type of acquired non-inherited sensorineural hearing loss, via disrupting the *Htra2* gene in the inner ear which is involved in apoptosis but has not been investigated in cochlear hair cell protection.

Results: The results indicate that adeno-associated virus (AAV)-mediated delivery of CRISPR/SpCas9 system ameliorates neomycin-induced apoptosis, promotes hair cell survival, and significantly improves hearing function in neomycin-treated mice. The protective effect of the AAV–CRISPR/Cas9 system in vivo is sustained up to 8 weeks after neomycin exposure. For more efficient delivery of the whole CRISPR/Cas9 system, we also explore the AAV–CRISPR/SaCas9 system to prevent neomycin-induced deafness. The in vivo editing efficiency of the SaCas9 system is 1.73% on average. We observed significant improvement in auditory brainstem response thresholds in the injected ears compared with the non-injected ears. At 4 weeks after neomycin exposure, the protective effect of the AAV–CRISPR/SaCas9 system is still obvious, with the improvement in auditory brainstem response threshold up to 50 dB at 8 kHz.

Conclusions: These findings demonstrate the safe and effective prevention of aminoglycoside-induced deafness via *Htra2* gene editing and support further development of the CRISPR/Cas9 technology in the treatment of non-inherited hearing loss as well as other non-inherited diseases.

Keywords: CRISPR/Cas9, Genome editing, Omi/HtrA2, Ototoxic deafness, Aminoglycoside antibiotics, Hair cell, Cochlea, Anti-apoptosis