On the Distant Horizon—Medical Therapy for Sensorineural Hearing Loss

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KEYWORDS

• Hearing loss • Gene therapy • Spiral ganglion neuron • Hair cell

KEY POINTS

- The inner ear has several structural and functional characteristics that make it an appealing target for novel gene therapy, RNA-based therapy, and stem cell therapy for treatment of sensorineural hearing loss (SNHL).
- The most rapid advancements have been in gene therapy; for example, a recent phase 1/2 clinical trial uses adeno-associated virus (AAV)-mediated delivery of atonal homolog 1 (*Atoh1*) to promote hair cell regeneration.
- Further research will be aimed at optimizing gene therapy expression and timing of delivery, promoting appropriate connectivity between engineered and endogenous cells, and exploring alternative techniques, such as genomic editing.

INTRODUCTION

Hearing loss is the most common sensory deficit in developed societies.[1,2] According to the Centers for Disease Control, 2 to 3 children out of every 1000 births have hearing loss.[3] Hearing impairment in children, particularly of prelingual onset, has been shown to negatively affect educational achievement, future employment and earnings, and even life expectancy.[4,5]

SNHL, which refers to defects within the cochlea or auditory nerve itself, far outweighs conductive causes for permanent hearing loss in both children and adults. The causes of SNHL in children are heterogeneous, including both congenital and acquired causes. In neonates in particular, a genetic cause accounts for half of all cases of hearing loss. Of those with genetic causes, 30% can be considered syndromic (eg, Pendred, Usher, Waardenburg) and the other 70% nonsyndromic. The inheritance pattern of nonsyndromic SNHL follows this general distribution: 75% autosomal

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Abbreviations

AAV	Adeno-associated virus
ABR	Auditory brainstem response
ASO	Antisense oligonucleotide
Atoh1	Atonal homolog 1
BDNF	Brain-derived neurotrophic factor
DFNA	Nonsyndromic deafness, autosomal dominant
DFNB	Nonsyndromic deafness, autosomal recessive
FGF	Fibroblast growth factor
GDNF	Glial cell line–derived neurotrophic factor
GJB2	Gap junction beta-2
HSV1	Herpes simplex virus 1
MYO7A	Myosin VIIA
NT-3	Neurotrophin 3
ONP	Oticlike neural progenitors
RNAi	RNA interference
SGN	Spiral ganglion neuron
SNHL	Sensorineural hearing loss
USH1C	Usher syndrome 1C

recessive, 20% autosomal dominant, 2%–5% X-linked, and less than 1% mitochondrial.[6] The mode of inheritance is important, as it guides the strategy of intervention, as explained in greater detail later.

The process of auditory transduction, in which mechanical sound waves are converted to electrical inputs, occurs at the level of the hair cell within the cochlea. The hair cell, located in the organ of Corti in mammals, contains specialized structures that project from the apical surface into the scala media and sense waves within the endolymph. The movement of these projections converts sound waves into electrical signals, which are subsequently carried via spiral ganglion neurons (SGNs) to the eighth cranial nerve. At any point along this pathway, a disruption in the conversion of mechanical signals to electrical signals propagated to the auditory nucleus results in SNHL. This article identifies potential mechanisms of intervention both at the level of the hair cell and the SGNs.

Approximately 16,000 hair cells are produced during early development in each cochlea, along with supporting cells and 30,000 to 40,000 afferent SGNs.[7] However, the fragile nature of hair cells makes them susceptible to damage and death because of genetic factors, exposure to noise, ototoxic drugs, and even early infection. Once damaged, these cells cannot be restored. However, since the discovery was made that avian species can spontaneously regenerate new hair cells after damage, translational research has been aimed at understanding this process so as to initiate a similar one in the human ear.[8]

Current treatment of SNHL cannot improve any cellular deficits; sound is either amplified with a hearing aid or the auditory nerve is stimulated with a cochlear implant. Both strategies use the remaining hair cells or auditory neurons. Yet, in recent years, new evidence suggests that future treatments may be able to improve SNHL at the cellular level through modification of hair cells or auditory neurons. These possible treatments follow 3 main approaches: (1) gene therapy to augment production of proteins that may protect or even regenerate hair cells, (2) RNA-based therapy to inhibit expression of detrimental proteins that promote hair cell damage, and (3) stem cell therapy to replace damaged or dead hair cells or auditory neurons. Although it is unlikely that any of these strategies will be a panacea for SNHL, they will add to the armamentarium of treatment options that can serve an individual patient.

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