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GENE THERAPY

Gene Therapy Boosts the Bionic Ear

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Close-field electroporation gene delivery using the cochlear implant electrode array enhances the bionic ear (Pinyon *et al.*, this issue).

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Hearing loss is a major health and economic burden on society. The World Health Organization estimates that over 5% of the world's population—360 million people—suffer from a disabling hearing loss (1). Hearing impairment can result in communication disorders, leading to educational, social, and vocational ramifications that can adversely affect quality of life. Hearing loss is also associated with dementia in the elderly. Sensorineural hearing loss is the most common form of deafness and typically occurs after the degeneration of cochlear hair cells that normally convert acoustic vibrations into nerve impulses within the primary cochlear afferents known as spiral ganglion neurons (SGNs) (Fig. 1, A and B). Patients with a severe-to-profound sensorineural hearing loss receive no benefit from amplification via a conventional hearing aid because of an absence of hair cells; the only therapeutic intervention available to these patients is a cochlear implant, or “bionic ear.” Now, Pinyon and colleagues offer the possibility of improved “bionic hearing” by modifying a cochlear implant to assist in gene therapy (2).

THE BIONIC EAR

Cochlear implants electrically stimulate SGNs in order to convey the spectral and temporal cues of speech. These devices contain an array of up to 22 platinum electrodes that are inserted into the scala tympani—a fluid-filled canal within the cochlea—to electrically stimulate discrete populations of SGNs. Cochlear implants take advantage of the tonotopic organization of the SGNs; stimulation of electrodes in the apex of the cochlea evokes low-pitch sensations, while stimulation of electrodes positioned more basally evoke higher pitches. Implanted in more than 300,000 patients around the world, cochlear implants are one of the most successful bionic devices developed; they are effective across the broad range of aetiologies associated with deafness and can be used in both adults and children.

Although cochlear implant recipients typically receive substantial benefit in speech understanding in quiet settings, bionic ear performance decreases in noisy environments. In addition, these devices do not convey the rich aural texture of music or tonal languages very well. A major reason for this reduced performance is the limited number of independent stimulation channels available owing to extensive current spread in the highly conductive, fluid-filled cochlea. This produces far broader neural activation of SGNs than does natural hearing, leading to a reduction in the fidelity of neural input to the auditory system. There are several approaches designed to improve the selectivity of electrical stimulation within the cochlea, including the use of current-focusing techniques to create more localized electrical fields and the use of drug-based therapies to improve the electrode-neural interface. For example, applying exogenous neurotrophins to the cochlea promotes SGN neurite growth toward the electrode array (3), resulting in reduced thresholds to electrical stimulation.

Pinyon *et al.* describe a new technique to deliver neurotrophins into the deaf cochlea using “close-field” electroporation (CFE) gene therapy (2). Electroporation is a means of transferring gene constructs into cells by increasing the permeability of the cell membrane through a series of brief but intense electric pulses. In this way, the authors were able to transduce mesenchymal cells lining the scala tympani of the cochlea with a complementary DNA (cDNA) gene construct designed to drive the expression of brain-derived neurotrophic factor (BDNF) (Fig. 1C). The authors adapted a commercially available cochlear implant electrode array to generate the localized high electric field necessary to achieve the electroporation-mediated gene delivery. They first evaluated the feasibility of the approach and optimized the electroporation parameters *ex vivo* in order to confirm that *BDNF* is delivered to the mesenchymal cells proximal to the electrode array.

Once proof of concept was demonstrated, the CFE approach was evaluated *in vivo* by using normal-hearing guinea pigs to again demonstrate the selective transduction of mesenchymal cells. The guinea pig cochlea has many anatomical features in common with the human inner ear and is widely used as an animal model of human disease in auditory research. Last, the experiment was repeated in deafened animals that were chronically implanted with an electrode array after electroporation (Fig. 1C). The electrode array was activated 2 weeks after gene delivery, and the electrically evoked auditory brainstem response was recorded to monitor the functional status of the SGNs. Importantly, the mean threshold of the *BDNF* treatment group was significantly lower than that of the control cohort, demonstrating an important functional advantage that has also been reported in the use of pump-based *BDNF* delivery techniques in animals (4–6). The observed functional advantage was consistent with the anatomical findings that show a significant increase in both SGN soma area and ectopic neurite outgrowth toward the electrode array in the *BDNF* group after a 2-week treatment period.

Taken together, these data show that the technique can result in an improved electrode-neural interface in deafened cochleae. It is anticipated that an improved interface will contribute to improved selectivity of electrical stimulation associated with cochlear implants. Greater selectivity of neural stimulation is expected to increase the fidelity of neural input to the auditory system, resulting in improved hearing outcomes.

CAN YOU HEAR ME NOW?

Hair cells are sensitive to many forms of pathology, including hereditary disorders, ototoxic chemicals, infections, noise exposure, and aging. Hair cells do not regenerate in mammals, and their loss initiates a sequence of pathological changes in SGNs that includes the retraction of spiral ganglion neurites from the organ of Corti (Fig. 1B) and atrophy of the SGN that may eventually lead to degeneration. These changes to SGNs reflect the loss of endogenous neurotrophic factors, including BDNF, that are normally expressed by hair cells and supporting cells of the organ of Corti. As noted, SGNs are the target neurons for cochlear implants; therefore, the degeneration of their peripheral neurites, or loss of the neuron itself, reduces the efficacy of the electrode-neural interface as the neuron retracts from the electrode array within the scala tympani (Fig. 1B). Over the past decade, researchers have been exploring safe and effective ways of delivering exogenous neurotrophins to the deafened cochlea with the specific objective of improving the electrode-neural interface. The study by Pinyon *et al.* (2) is an important contribution to this work.

Although the inner ear has been a target for drug-based therapies for over 60 years via systemic or middle-ear routes, direct application to the cochlea has only been recently used clinically and is restricted to patients with a moderate to severe hearing loss in which the risk of further damage to their hearing is reduced. These delivery techniques are usually designed to be performed in association with cochlear implantation because the scala tympani is already surgically exposed for the implantation of the electrode array. Techniques evaluated to date in preclinical studies include drug elution from an electrode array carrier; drug release from a reservoir and cannula within the electrode array; viral-mediated gene therapy; cell-based therapies; and nanotechnology-inspired release, either as a polymer coating on the electrode array or via slow release particles that are inserted into the cochlea just before or after the insertion of the electrode array (7–9). Although several of these techniques have demonstrated SGN rescue and functional evidence of an improved electrode-neural interface, some also bring potential clinical complications, such as the risk of infection associated with a drug reservoir and cannula system. Clinical trials not involving the delivery of neurotrophins are about to commence using drug elution from an electrode array and viral-mediated gene delivery techniques.

NEURONAL RESCUE

Pinyon *et al.* demonstrated both neurite growth into the scala tympani in the proximity of the electrode array and improved bionic hearing in the form of reduced electrical thresholds, using a technique and device that are transferrable to the clinic. However, several important questions still remain. First, long-term efficacy of the approach is unknown. The authors demonstrated neurite regrowth and functional advantage in the first 2 weeks after the treatment but described a reduction in *BDNF* expression over the 3 to 6 weeks after the gene delivery period. A key question associated with the efficacy of this technique is the duration of any functional advantage after loss of the neurotrophin expression. To this end, there is evidence that chronic depolarization of SGNs potentiates the rescue effects of exogenous neurotrophins (6); therefore, the long-term efficacy of this

technique needs to be evaluated in concert with chronic electrical stimulation via a cochlear implant.

In addition, the longevity of mesenchymal cells that take up the plasmid is unknown, as is their status after a long-term hearing loss. Studies to evaluate the turnover of these cells in experimental animals and their status in human cochleae are necessary. Furthermore, techniques designed to improve the longevity of *BDNF* expression and methods that allow targeting of other cells within the cochlea also need to be explored.

This new work describes ectopic sprouting of SGN neurites in response to the BDNF treatment. This is a common finding associated with exogenous delivery of neurotrophins that has raised concerns about the maintenance of the cochlea's tonotopic organization. Although evidence to date indicate that this organization is not adversely affected (10), additional long-term experiments are warranted.

Last, in the study by Pinyon *et al.* the stimulus parameters that delivered optimal gene delivery were well beyond the specifications of a modern cochlear implant. To translate this technology to the clinic, stimulus parameters for effective electroporation need to be explored within the constraints of the specifications of the cochlear implant stimulator.

These questions aside, this new work presents a novel gene delivery technique to regenerate SGN neurites and improve hearing outcomes for cochlear implant users. The method is readily translatable to the clinic, requiring only a minor modification in surgical procedure—the delivery of a small volume of plasmid to the cochlea followed by a brief period of stimulation to drive the gene transfer. One exciting outcome is the potential to apply the technique to other medical bionics applications, such as retinal prostheses and deep brain stimulation. Like cochlear implants, these devices electrically stimulate damaged nerves. Therefore, the safe and local application of therapeutic genes or drugs delivered via electroporation could improve the clinical outcomes for patients using a wide variety of prosthetic devices.

Fig. 1. Boosting bionic hearing. Gene therapy could improve the fidelity of bionic hearing by stimulating neurite regrowth toward the electrode array. **(A)** Schematic showing a section of normal cochlea with an intact organ of Corti containing the sensory hair cells and spiral ganglion neuron (SGN) soma and their neurites that synapse onto the hair cells. A single cell layer of mesenchymal cells lining the cochlea is also illustrated. **(B)** The organ of Corti degenerates after a sensorineural hearing loss, inducing the neurites to retract and some SGNs to degenerate. Patients with a widespread loss of hair cells receive no benefit from amplification via a hearing aid; the only therapy available is a cochlear implant in which an electrode array is inserted into the scala tympani in order to directly stimulate SGNs. **(C)** Pinyon *et al.* injected a DNA construct that contained the *BDNF* gene into the cochlea. *BDNF* was taken up by mesenchymal cells lining the scala tympani (green) using electroporation via the cochlear implant electrode array. Ectopic neurite projections toward the electrode array were observed in concert with a reduction in electrical thresholds.

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