Halting the Progression of Noise-Induced Hearing Loss with Gene Therapy

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AIM

To establish the efficacy of BDNF and Atoh1 gene therapy on hair cell and hearing protection in a progressive noise-induced hearing loss model.

INTRODUCTION

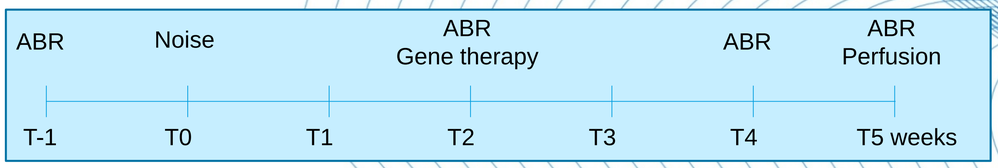
Progressive hearing loss is often ignored until there is significant loss of cochlear hair cells (HCs) and spiral ganglion neurons (SGNs). It usually begins as a mild high-frequency threshold shift which worsens and also spreads to the lower frequencies. Our previous research indicated that gene therapy is effective for long-term preservation of SGNs when administered shortly after *ototoxic* hearing loss, but has greater potential to protect residual HCs and SGNs after the onset of *progressive* hearing loss and even to restore hearing.

METHODS

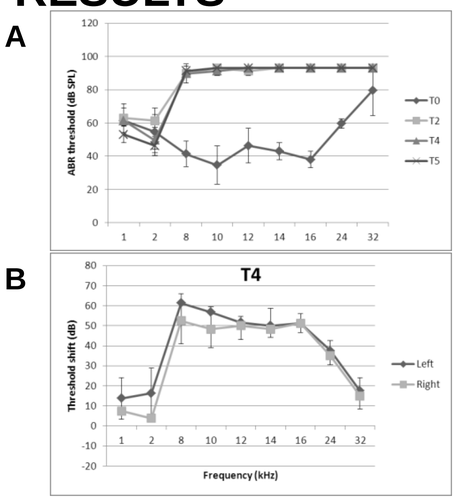
Normal hearing guinea pigs were exposed to 130 dB closed-field noise for 2 hours (10-14 kHz) under anaesthesia (n=15). Two weeks later, gene therapy was given by injection of adenoviral vectors expressing GFP with or without the genes for brain derived neurotrophic factor (BDNF) or Atoh1 into the scala media of the left cochlea. Three weeks later the cochleae were examined for gene expression, HC survival and neural connectivity. Hearing was monitored by tone pip auditory brain-stem response (ABR) recordings at several time points throughout.

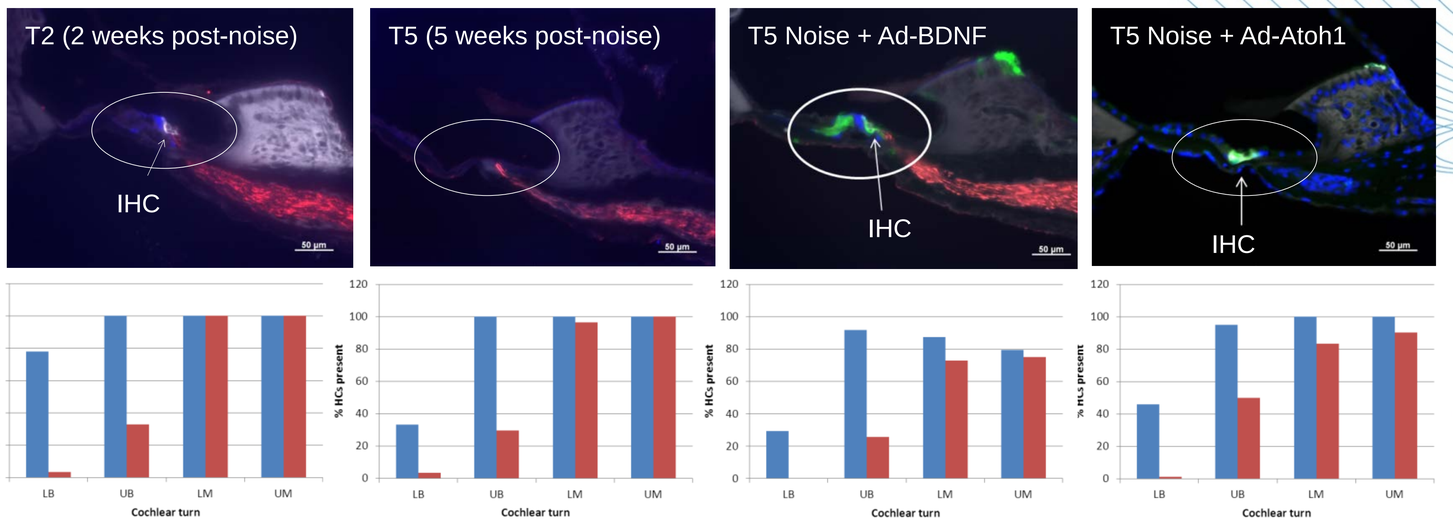
GROUPS

- Deaf only (2 and 5 wk)
- Deaf + Ad-GFP
- Deaf + Ad-BDNF
- Deaf + Ad-Atoh1



RESULTS





White = Myosin VIIa (HCs)
Red = Neurofilament (neurons)
Green = GFP (gene therapy)
Blue = phalloidin (supporting cells) in first 3 images and DAPI (nuclei) in last image)

LB = lower basal
UB = upper basal
LM=lower middle
UM = upper middle
IHC = inner hair cell
OHC = outer hair cell

A. ABR threshold (1-32 kHz) for the 5 week deaf only (non-injected) group. There is a significant threshold shift 2 weeks after noise exposure (T2) (8-24 kHz $p<0.05$) that remains elevated at T4 and T5. **B.** In the gene therapy groups, there is a significant difference between left (injected) and right (non-injected) ears at T2 (at 2 and 8 kHz) ($p<0.05$) indicating that the scala media surgical approach results in minor hearing loss.

Images show the left cochlea organ of Corti (circled) in the lower basal turns of the 2-week deaf, 5-week deaf, Ad-BDNF and Ad-Atoh1 gene therapy groups. Corresponding graphs show inner and outer HC numbers in the basal and middle turns. At T2 (2 weeks post noise-exposure), most IHCs are still present while OHCs in the lower and upper basal turns have died. At T5, more IHCs have been lost but there was not much change in OHCs. Ad-BDNF gene therapy resulted in BDNF expression in the basal turn of the cochlea (green). There was IHC and OHC survival in regions adjacent to BDNF expression as well as survival of supporting cells of the organ of Corti (blue). Ad-Atoh1 gene therapy resulted in Atoh1 expression in the basal turn of the cochlea. In some cases, cells that expressed Atoh1 also expressed the HC marker myosin VIIa indicative of transformation of a supporting cell into a new HC. Supporting cell survival was poorer in this group compared to the Ad-BDNF group. There was no overall improvement in IHC or OHC numbers in the gene therapy groups compared to the non-injected cochleae due to some loss of HCs from the injection procedure.

CONCLUSIONS

Gene therapy in the scala media of the cochlea is well suited to a progressive hearing loss model as it targets the high frequency region of the cochlea and requires intact HCs and supporting cells for transduction. HCs are protected or regenerated by BDNF or Atoh1 gene therapy after noise-induced hearing loss. However, the HC protection does not overcome the loss of HCs caused by the scala media injection and a new surgical approach is required.

Acknowledgements

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