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STOCKBYTE

AUDITORY SYSTEM

Turn it up a notch

Hearing loss due to damaged auditory hair cells is thought to be irreversible as these cells do not regenerate. Now, for the first time, Edge and colleagues have used a pharmacological approach to generate new hair cells and partially restore hearing in mice after acoustic trauma.

During development, Notch signalling is known to prevent supporting cells from differentiating into hair cells, and *in vitro* studies have shown that inner ear stem cells can generate hair cells when treated with a γ-secretase inhibitor that prevents Notch signal transduction. In an assay of inner ear stem cell differentiation into hair cells, the authors identified LY411575 as a potent γ-secretase inhibitor. This inhibitor was also found to increase the number of hair cells, which was assessed by the increase in cells expressing the hair cell-specific marker myosin VIIa, in organ of Corti explants from both neonatal wild-type and transgenic mice subjected to hair cell ablation. Furthermore, in the mature ear of mice exposed to an acoustic injury that produces widespread hair cell death and permanent hearing loss, systemic administration of the inhibitor increased the number of hair cells.

Owing to the severe side effects observed when the inhibitor was administered systemically, further *in vivo* studies involved localized delivery of LY411575 to the inner ear 1 day after noise exposure. Using RT-PCR, the authors were able to show that acoustic injury leads to an increase in *Hes5* mRNA expression (a direct downstream target of Notch) and that local γ-secretase inhibitor treatment blocked this activation, resulting in sustained upregulation of *Atoh1* mRNA, which encodes a transcription factor that is required for hair cell differentiation.

> “administration of the inhibitor increased the number of hair cells in the mature ear of mice exposed to an acoustic injury”

In vivo lineage tracing experiments and the analysis of hair cell markers demonstrated that the new hair cells that arise following the noise-induced injury derive from the trans-differentiation of supporting cells from the apical to the mid-apical turn in the cochlea. Importantly, the response thresholds in the auditory brainstem, which projects to the cochlea, were lower in LY411575 treated animals than controls, and the recovery lasted for at least 3 months. Although this approach may be limited to treatment of acute hearing loss shortly after damage, local drug administration represents a more attractive strategy than gene therapy.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPER Mizutari, K. *et al.* Notch inhibition induces cochlear hair cell regeneration and recovery of hearing after acoustic trauma. *Neuron* **77**, 58–69 (2013)