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Preservation and Regeneration of the Auditory System

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Interventions to prevent cochlear sensorineural cell death as well as regrowth and regeneration of these cells may provide future drug treatments for prevention and treatment of deafness. Recent studies have shown that noise-induced and drug-induced hearing loss and the associated sensory cell death may be prevented with agents that prevent or scavenge free radicals, prevent excitotoxicity, increase blood flow or inhibit cell death pathways. Following loss of sensory cells, deafferentation, as with other nerves, the auditory nerve degenerates. Studies have shown that nerve growth factors and electrical stimulation may rescue spiral ganglion cells from deafferentation-induced death. We have extended these studies to assess the efficacy of these factors to regrow the auditory nerve. We find that both neurotrophic factors and electrical stimulation cause a robust regrowth of afferent processes. Regrown fibers are directed into the region of the organ of Corti, as well as into the scala tympani, which may have significant implications for a closer integration of cochlear implants with the auditory nerve. Most recently we examined the use of stem cells to replace the auditory nerve, for those patients in which the rescue from cell death or regrowth is no longer possible. In this first study we tested if influences that guide auditory nerve differentiation during normal development can induce mouse embryonic stem cell (mESC) differentiation to an auditory nerve-like phenotype in vitro and in vivo. For in vitro assessment, 48h expression of neurogenin 1, a proneural gene associated with early auditory nerve differentiation was combined with application of Brain Derived Neurotrophic Factor (BDNF) and Glial cell-line Derived Neurotrophic Factor (GDNF), neurotrophic factors also involved in the auditory nerve fate choice. For in vivo studies, mESCs were placed into scala tympani and modiolus of guinea pig cochleae four - five weeks following deafening and 48h of in vivo neurogenin 1 induction was followed by 14 days chronic intrascalar infusion of BDNF and GDNF. With either in vitro or in vivo differentiation, approximately 70% of mESC reach a neuronal phenotype, based on TUJ1 immunostaining. The majority of these had an auditory nerve-like glutamatergic phenotype based on vesicular glutamate transporter immunostaining. Controlled transient induction of genes important in determining developmental spiral ganglion cell fate may provide an important tool in the use of stem cells to replace the auditory nerve.

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