AUDITORY SYSTEM

Senses working overtime

The act of hearing involves not only identifying the nature of a sound, but also pinpointing the location of its source. To achieve this, the brain needs to compare the sounds received by the two ears, and this requires the development of ear-specific processing circuits. As in other sensory systems, peripheral neuronal activity is thought to play an instructive role in the patterning and refinement of these circuits. In the auditory system, it was previously thought that this activity was derived only from cells that were actively responding to sound. However, as reported in the *Journal of Neuroscience*, Jones *et al.* have now shown that during development, cochlear neurons can exhibit spontaneous activity in the absence of external sensory input.

The authors measured the activity of cochlear ganglion cells in chick embryos between embryonic days 13 and 17. They showed that a high proportion of the cells exhibited rhythmic bursting activity. Bursting cells were most prevalent in the embryos at the younger end of the age range, although the rate of bursting in individual cells increased as development progressed. The bursting patterns became less regular with time, indicating that spontaneous rhythmic bursting is a transient phenomenon. Of 18 cells that showed rhythmic bursting, only five were able to respond to sound.

Activity-dependent development has been extensively studied in the visual system, where it is likely that spontaneous neuronal activity plays a significant role in the patterning of cortical circuits. It is to be hoped that future studies will show whether the spontaneous bursting activity detected by Jones *et al.* in the cochlea has a similar influence on the development of auditory processing circuits.

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References and links

ORIGINAL RESEARCH PAPER Jones, T. A. *et al.* Primordial rhythmic bursting in embryonic cochlear ganglion cells. *J. Neurosci.* **21**, 8129–8135 (2001)

FURTHER READING Katz, L. C. & Shatz, C. J. Synaptic activity and the construction of cortical circuits. *Science* **274**, 1133–1138 (1996)

NEUROTECHNIQUE

Creating the perfect blend

During the development of the nervous system, the fate of neural progenitor cells is influenced by the microenvironment they experience — a particular combination of adhesion cues, extracellular matrix and growth factors such as the neurotrophins. At present, there is considerable hope that transplanted neural progenitor cells can be harnessed to restore function within degenerated regions of the central nervous system in disorders such as Parkinson's disease. For this to work, the transplanted cells must differentiate and form synaptic contacts with the surrounding tissue. However, adult nervous tissue is a relatively unfavourable environment for cell migration, differentiation and axonal growth, owing to the presence of inhibitory molecules such as myelin-associated glycoprotein. Nervous tissue regeneration can be promoted by increasing the levels of neurotrophins, but these factors potently influence other cellular functions apart from survival and growth, which means that systemic administration can lead to broad, adverse side effects. Writing in *Nature Biotechnology*, Mahoney and Saltzman now describe a strategy with the potential to address these issues. By pre-assembling neural progenitor cells with controlled-release microparticles containing nerve growth factor (NGF) to give transplantable "neo-tissues", aspects of the extracellular environment experienced by progenitor cells during development can be mimicked directly at the transplantation site.

Controlled-release microparticles were formed by encapsulating NGF — which influences the survival and growth of cholinergic neurons — in biocompatible polymers, and were then assembled with fetal rat brain cells in rotational culture to give spherical neo-tissues ~170 μm in diameter. By using microparticle preparations known to release NGF at different rates, neo-tissues with different microenvironments were created. NGF levels in the different neo-tissues and in the surrounding medium after 4 days in culture correlated with the NGF release rate of the particular microparticles; a similar trend in the levels of choline acetyltransferase (ChAT) activity, a marker of cholinergic neuron function, was also observed in the neo-tissues.

Next, the authors transplanted the neo-tissue with the highest NGF release rate into the brains of healthy adult rats to assess the functional activity *in vivo*. Transplanted cells remained aggregated at the site of injection throughout the 21-day experiment. NGF levels were significantly elevated at this site for the first 7 days, but fell off subsequently, presumably owing to exhaustion of the NGF source. But ChAT activity was elevated for the entire course of the experiment, indicating that NGF is released from the microparticles at levels sufficient to influence cholinergic cell survival and/or differentiation over the period of study.

So, the techniques that Mahoney and Saltzman describe allow the creation of synthetic microenvironments in which several variables of potential importance to cell survival and differentiation — position of growth factor source, growth factor dose and molecular signals at the cell surface — can be controlled. Such neo-tissues containing combinations of microparticles, each releasing a molecule that promotes a particular aspect of transplanted cell function (for example, an antibody to the inhibitory myelin-associated glycoprotein), could be useful in treating neurodegenerative diseases and spinal cord injuries.

Peter Kirkpatrick, Associate Editor,
Nature Reviews Drug Discovery

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WEB SITE
Saltzman lab: http://www.cheme.cornell.edu/peopleevents/faculty/saltzman/