Nature Reviews Neuroscience | AOP, published online 10 May 2011; doi:10.1038/nrn3265

NEURODEGENERATIVE DISORDERS

Transplanted photoreceptors see the light

Cell transplantation is a possible treatment strategy for blindness caused by retinal degeneration. Although it has been shown that transplanted photoreceptor cells can differentiate and acquire a mature photoreceptor phenotype, whether these cells integrate into retinal circuits to produce a functional improvement in vision is uncertain. A study by Pearson *et al.* now demonstrates restored vision in a genetic mouse model of blindness following rod-photoreceptor transplantation.

The authors used a murine model of stationary night blindness in which rod-photoreceptor function had been ablated through knockout of α-transducin (GNAT1), a protein essential for phototransduction in these cells. They then harvested rod precursor cells for transplantation from neonatal mouse retinae, having identified the cells using green fluorescent protein as a marker of rod photoreceptors (under control of the rod-specific transcription factor neural retina-specific leucine zipper protein (NRL)). The authors used optimized transplantation procedures that involved subretinal injection of the donor cells into both the superior and the inferior retina of *Gnat1*$^{-/-}$ mice and obtained levels of photoreceptor integration that were 20–30-fold higher than their previous transplantation studies.

Morphological and functional characterization of the integrated cells showed that they expressed mature rod markers and were morphologically similar to wild-type rod photoreceptors. Like wild-type rods, the transplanted cells were located in the outer nuclear layer of the retina, and most had synaptic boutons expressing rod ribbon synapse proteins such as ribeye, bassoon and dystrophin. Wild-type rods form a classic triad synapse with retinal second-order bipolar and horizontal cells, and ultrastructural analysis confirmed transplanted rod photoreceptors to have formed a similar arrangement.

Next, the authors tested the light responses of integrated transplanted rods using suction-pipette recordings of individual integrated rods. They found that these cells responded to light in a similar way to wild-type rods. They reasoned that if the rods had properly integrated into retinal circuits, then signals from these cells would be transmitted to visual cortex. Indeed, stimulation of each eye using dim flickering black and white bars on a grey background evoked strong responses in visual cortex of wild-type mice and *Gnat1*$^{-/-}$ mice that had received rod transplants, but not in untreated *Gnat1*$^{-/-}$ mice.

The most important question, however, was whether vision had been improved by transplantation. To test this, the authors monitored whether the transplanted mice reflexively moved their heads in the direction of a rotating grating. *Gnat1*$^{-/-}$ mice exhibited no head-tracking behaviour, whereas mice that had received transplanted rod photoreceptors did. Furthermore, in a visually guided water-maze test — used to assess cognitive processing of visual information — only wild-type mice and *Gnat1*$^{-/-}$ mice receiving rod transplants were able to solve the task, whereas untreated *Gnat1*$^{-/-}$ mice could not. In both behavioural tests, performance was correlated with the number of integrated rod photoreceptors. Overall, these findings show that in mice, at least, retinal transplantation can restore vision.

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ORIGINAL RESEARCH PAPER Pearson, R. A. *et al.* Restoration of vision after transplantation of photoreceptors. *Nature* 18 Apr 2012 (doi:10.1038/nature10997)