SENSORY SYSTEMS

# Back into the light

Retinal degeneration is characterized by the progressive loss of rod and cone photoreceptors. Two studies now show that reactivation of surviving retinal cells by expression of exogenous rhodopsins using gene therapy can restore the function of visual circuits, but that the success of this strategy depends on the cell population being targeted.

Thyagarajan *et al.* crossed transgenic mice that expressed the microbial light-activated channel channelrhodopsin 2 (ChR2) with an established mouse model for retinal degeneration (*rd1*/*rd1*). In the offspring, 30–40% of retinal ganglion cells expressed ChR2 and responded to light stimuli. All of these cells were depolarized in response to a light stimulus. This contrasts with ganglion cells in wild-type retinas, half of which normally respond to a light stimulus ('ON' cells) and the other half to a dark stimulus ('OFF' cells). As these subpopulations are spatially segregated, this determines the structure of the cortical receptive fields. Behavioural testing of the visual performance of the transgenic mice revealed that they could discriminate between light and dark fields, but their performance in more sophisticated visual tasks did not differ from that shown by *rd1* mice. The authors speculated that the loss of specific synaptic inputs caused by retinal degeneration made the response of the ganglion cells to visual stimuli too homogeneous. This might have disrupted the structure of cortical cell receptive fields and prevented the successful decoding of visual information in the cortex.

Busskamp *et al.* targeted light-insensitive cone photoreceptors (which characterize intermediate stages of retinal degeneration) with an adeno-associated virus to express the light-activated chloride pump halorhodopsin in retinas from two mouse models of retinal degeneration. Cones expressing the exogenous rhodopsin exhibited larger and faster photocurrents compared with wild-type cones. Remarkably, both increases and decreases in light intensity elicited excitatory currents in the ganglion cells that formed synapses with the cones expressing halorhodopsin. This implies that this experimental approach preserves the heterogeneity in the ganglion cell response that occurs in a healthy retina. Furthermore, some of the ganglion cells responded preferentially to bar-shaped stimuli that moved in a particular direction, which suggests that the retinal circuit for directional selectivity was intact. Mice expressing the exogenous rhodopsin performed better than the control group in several tests of visually guided behaviour. This demonstrates that re-sensitized photoreceptors can compensate for the loss of retinal cells.

These results show that gene-targeting therapies can be used to restore photosensitivity to retinas after degeneration. However, targeting the expression of the exogenous light sensor to the appropriate cell population is key for success. In particular, preserving the pattern of synaptic inputs from photoreceptors to ganglion cells seems essential to maintain some basic retinal functions. Further studies will determine whether these promising results can be translated into an effective therapeutic strategy for patients who are affected by neural degeneration.

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**ORIGINAL RESEARCH PAPERS** Thyagarajan, S. *et al.* Visual function in mice with photoreceptor degeneration and transgenic expression of channelrhodopsin 2 in ganglion cells. *J. Neurosci.* **30**, 8745–8758 (2010) | Busskamp, V. *et al.* Genetic reactivation of cone photoreceptors restores visual responses in retinitis pigmentosa. 24 Jun 2010 *Science* (doi: 10.1126/science.1190897)