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# Neurotrophic Rescue of Photoreceptors: Are Müller Cells the Mediators of Survival?

Neuronal death in the retina has been studied not only because of its own biological importance and its relevance to clinical disease, but also because retinal apoptosis serves as a model system for death elsewhere in the central nervous system (Nickells and Zack, 1996). Neurodegenerative retinal diseases in which apoptosis has been implicated include photoreceptor degenerations such as retinitis pigmentosa and age-related degeneration, retinal ganglion cell diseases such as glaucoma and other optic neuropathies, and more panretinal diseases like diabetic retinopathy. In an effort to develop novel treatment approaches for these diseases, various anti-apoptotic strategies have been explored. Transgenically engineered overexpression of bcl-2 in retinal ganglion cells leads to an inhibition of developmental apoptosis and relative resistance of ganglion cells to toxic insults such as optic nerve axotomy. Although more controversial, some results suggest that bcl-2 overexpression can also protect photoreceptors from damage (Chen et al., 1996). Perhaps more promising from a clinical point of view, neurotrophic factors, which inhibit neuronal apoptosis in a wide variety of systems, inhibit ganglion and photoreceptor cell death both in vitro and in vivo (Steinberg, 1994; LaVail et al., 1998).

The mechanism by which neurotrophic factors protect photoreceptor cells from degeneration is unclear. Control of neuronal survival by neurotrophins is generally mediated by two types of receptors: the Trk family of high-affinity tyrosine kinase receptors (TrkA, B, and C), which usually transmit a prosurvival signal, and the neurotrophin receptor $p75^{NTR}$, which transmits an anti-survival signal (Casaccia-Bonnefil, 1999). A paradox in the photoreceptor field is that although brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) have been consistently reported as neuroprotective for rod photoreceptor cells, thus suggesting that the corresponding receptors, TrkB and CNTFR$\alpha$, are expressed by these cells, most studies have thus far failed to find evidence that mammalian rods express either TrkB or CNTFR$\alpha$ (Ugolini et al., 1995; Kirsch et al., 1997). As a result, it has been proposed that neurotophic rescue of photoreceptors may be indirect, mediated by interaction of the neurotrophic factor with a nonphotoreceptor cell type that in turn releases a secondary factor, or perhaps by a cell contact–mediated mechanism. Several lines of evidence suggest that the Müller cell may be an important player in this indirect rescue mechanism. Müller cells are the predominant glial element in the retina, and they carry out many of the functions provided by astrocytes, oligodendrocytes, and ependymal cells elsewhere in the CNS (Newman and Richenbach, 1996). Müller cells contain receptors for most of the molecules that have been shown to rescue photoreceptors; they become stimulated, as indicated by the expression of glial fibrillary acidic protein (GFAP), in response to a variety of toxic stimuli, including retinal degeneration (Ekstrom et al., 1998); transgenic experiments suggest that loss of Müller cells leads to photoreceptor death (Dubois-Dauphin et al., 2000); and Müller cells, but not photoreceptors, are consistently activated by intraocular administration of BDNF, CNTF, and basic fibroblast growth factor (FGF2), as measured by increased expression of the immediate-early protein c-*fos* and the phosphorylated form of the extracellular signal–regulated kinase (pERK) (Wahlin et al., 2000).

Although suggestive of a role for Müller cells in protecting photoreceptor cells from apoptosis, all of the data just cited is itself indirect and fails to provide much insight as to the mechanism by which Müller cells might rescue photoreceptors. Harada et al. (2000), in this issue of *Neuron*, present new information that provides more direct support for the Müller cell hypothesis and suggests involvement of the low-affinity $p75^{NTR}$ neurotrophin receptor in photoreceptor death in the adult retina. (Previous work had already implicated $p75^{NTR}$ in cell death during retinal development [Casademunt et al., 1999].) Using the phototoxicity model of retinal degeneration, in which high-intensity and/or prolonged light exposure leads to photoreceptor cell loss, they show that degeneration is associated with an increase in Müller cell expression of $p75^{NTR}$ and TrkC, and induction of TrkC expression by photoreceptor cells. Administration of exogenous NT-3, which is photoreceptor cell protective, increased Müller cell production of FGF2, while NGF decreased its production. Functionally, they demonstrate that presumptive antibody-mediated blockade of $p75^{NTR}$ signaling prolongs photoreceptor survival. Most significantly, they show that in *$p75^{NTR}$* null mice there is a decrease in photoreceptor injury following light exposure. Putting this all together, the authors suggest a model in which there is a fine balance between pro- and antiapoptotic forces: Müller cells, acting in response to exogenous NT-3 or NGF via TrkC or $p75^{NTR}$ receptors, respectively, increase or decrease their production of the photoreceptor survival factor FGF2, which in turn results in either the protection of photoreceptor cells or increased apoptosis. In addition, since light-damaged photoreceptors express TrkC, NT-3 may also act directly upon injured photoreceptors. Interestingly, a similar glial–neuronal interaction model has been proposed for the mechanism by which BDNF promotes retinal bipolar cell survival in vitro (Wexler et al., 1998).

An important innovation in the work by Harada et al. is the use of laser capture microdissection (LCM) for the study of gene expression in subtypes of retinal cells. Using LCM in conjunction with RT–PCR, they succeed in measuring gene expression differences between photoreceptors and inner nuclear layer cells. Although not fully exploited in this study, LCM has the potential to allow study of complex patterns of gene expression between neighboring and interacting cell populations. In a recent study, LCM was combined with cDNA microarray analysis to compare the in vivo gene expression profiles of large and small dorsal root ganglia neurons

(Luo et al., 1999). This approach will be particularly useful to correlate functional and gene expression changes within small regions of the retina, and, since much of retinal disease is focal, to compare neighboring regions of normal versus diseased tissue.

As impressive and suggestive as the results of Harada et al. are, it is worth considering some potential caveats before extending their results too broadly. The specificity of the immunological and pharmacological blocking reagents used in the study is good, but not absolute. The light toxicity model is only one of many available retinal degeneration models, including naturally occurring mouse mutants (such as *rd*); mouse, rat, and pig transgenic models; and an increasing number of knockout models. In fact, photoxicity is considered by some in the field to be one of the less physiological models. Although all models examined seem to share apoptosis as the final common pathway of photoreceptor death, it is now abundantly clear that apoptosis is not a single, simple pathway. There are significant differences between the various photoreceptor degeneration models, and even species differences within the same model. As one example, photoreceptors in mice that are null for the c-*fos* gene are relatively resistant to light damage but die just like wild-type cells in the *rd* model (Hafezi et al., 1998). As another example, the effectiveness of neurotrophins as rescue agents varies significantly between mammalian species. Thus, it will be important to directly test whether the results of Harada et al. do indeed extend to other models and other species, and it will be particularly interesting to determine whether the $p75^{NTR}$ null mice are resistant to other forms of retinal degeneration. Regardless of the results, however, it is clear that this piece of work will help focus interest on the importance of glial–neuronal cell interactions within the retina, and in the role these interactions may play in degenerative diseases of the retina.

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