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Long-term neuroprotection in an optic nerve axotomy model using recombinant Adeno Associated Virus (rAAV)

In this study, we used the optic nerve transection model to study neuroprotection by expressing different neurotrophic and anti-apoptotic proteins using rAAV. Transection of the optic nerve results in degeneration of 85-90% of RGC within 14 days. We demonstrated that overexpression of Bcl-xl resulted in survival of 85% of RGC for a period of 14 days after axotomy. Co-expression of GDNF and Bclxl protected more than 95% of the RGC during the same period. Long-term protection studies showed that Bcl-xl could preserve 41% of RGC for up to 8 weeks and a combination of GDNF and Bcl-xl promoted survival of nearly 68% of RGC after axotomy. We could also show that the axons of the surviving RGC axons remained morphologically intact after the lesion thus providing a basis for regeneration. Here, we also demonstrated a long lasting, highly efficient and specific downregulation of a reporter gene in the RGC. This is the first evidence of a cell typespecific RNAi in the eye, which is a prerequisite for the use of this technique for future neuroregenerative studies of the optic nerve. For ongoing studies, we propose to knock down RhoA, a key-signaling molecule preventing neurite outgrowth, and promote optic nerve regeneration.