

Astrocyte-derived SPP1 prevents age- and glaucoma-related loss of vision



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Glaucoma is characterized by the progressive loss of retinal ganglion cells, the neurons that connect the retina to the visual centers in the brain. The main risk factors are age, elevated intraocular pressure (IOP), and genetic factors. Currently, the mainstay of glaucoma therapy is lowering IOP, but this is not successful in all cases. Thus, alternative neuroprotective therapies are needed.

Experimental evidence shows that the first signs of ganglion cell degeneration occur in the optic nerve head, where the ganglion cell axons exit the globe to form the optic nerve. In this region, the axons come into direct contact with astrocytes, a type of supporting glial cell in the central nervous system. Optic nerve astrocytes react to many types of injury—including elevated IOP—with changes in their morphology and gene expression pattern. This astrocyte reactivity is a protective response that aims to re-establish equilibrium and prevent further damage to the ganglion cells (at least in the early stages of glaucoma). This suggests that astrocytes, or astrocyte-derived factors, could be used as a neuroprotective therapy for glaucoma and potentially other neurodegenerative diseases.

Using RNA sequencing, we have identified genes that are upregulated after damage to the optic nerve and screened several of them for neuroprotective activity. One of our leading candidates is a cytokine-like factor called SPP1, which is produced by astrocytes after optic nerve injury. Further investigation in animal models of glaucoma revealed that overexpressing SPP1 in the retina and optic nerve results in robust protection of retinal ganglion cells and visual function. Long-term expression of SPP1 slows the normal age-dependent loss of retinal ganglion cells in all mammalian retinas and, moreover, is apparently well tolerated and does not cause negative side effects in the eye. This suggests that the SPP1 protein may be a promising protein drug candidate for neuroprotection in glaucomatous and aging eyes.