Interleukin-6 Deficiency Attenuates Retinal Ganglion Cell Axonopathy and Glaucoma-Related Vision Loss

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The pleotropic cytokine interleukin-6 (IL-6) is implicated in retinal ganglion cell (RGC) survival and degeneration, including that associated with glaucoma. IL-6 protects RGCs from pressure-induced apoptosis in vitro. However, it is unknown how IL-6 impacts glaucomatous degeneration in vivo. To study how IL-6 influences glaucomatous RGC axonopathy, accompanying glial reactivity, and resultant deficits in visual function, we performed neural tracing, histological, and neurobehavioral assessments in wildtype (B6;129SF2/J; WT) and IL-6 knock-out mice (B6;129S2-IL6tm1kopf/J; IL-6-/-) after 8 weeks of unilateral or bilateral microbead-induced glaucoma (microbead occlusion model).

IOP increased by 20% following microbead injection in both genotypes (p < 0.05). However, deficits in wound healing at the site of corneal injection were noted. In WT mice, elevated IOP produced degenerating axon profiles and decreased axon density in the optic nerve by 15% (p < 0.01). In IL-6-/- mice, axon density in the optic nerve did not differ between microbead- and saline-injected mice (p > 0.05) and degenerating axon profiles were minimal. Preservation of RGC axons was reflected in visual function, where visual acuity decreased significantly in a time-dependent manner with microbead-induced IOP elevation in WT (p < 0.001), but not IL-6-/- mice (p > 0.05). Despite this preservation of RGC axons and visual acuity, both microbead-injected WT and IL-6-/- mice exhibited a 50% decrease in anterograde CTB transport to the superior colliculus, as compared to saline-injected controls (p < 0.01).

Assessment of glial reactivity revealed no genotype- or IOP-dependent changes in retinal astrocytes. IOP elevation decreased microglia density and percent retinal area covered in WT mice (p < 0.05), while IL-6-/- mice exhibited only a decrease in density (p < 0.05). Together, our findings indicate that two defining features of RGC axonopathy-axon transport deficits and structural degeneration of axons-like occur via independent mechanisms. Our data suggest that IL-6 is part of a mechanism that specifically leads to structural degeneration of axons.

Furthermore, its absence is sufficient to prevent both structural degeneration of the optic nerve and vision loss. Overall, our work supports the proposition that functional deficits in axon transport represent a therapeutic window for RGC axonopathy and identify IL-6 signaling as a strong target for such a therapeutic.


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