

Membrane-bound Fas-ligand induces retinal ganglion cell death associated with glaucoma

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Glaucoma, the most frequent optic neuropathy, is a leading cause of blindness worldwide. Death of retinal ganglion cells (RGCs) occurs in all forms of glaucoma and accounts for the associated loss of vision, however the molecular mechanisms that cause RGC loss are largely unknown. The pro-apoptotic molecule, Fas ligand, is a type II transmembrane protein that can be cleaved from the cell surface by metalloproteinases to release a soluble protein with antagonistic activity. Previous studies have documented constitutive ocular expression of FasL as a means to maintain immune privilege and prevent neoangiogenesis, but whether these functions are mediated by the full-length or soluble forms of FasL is unresolved. We now show that FasL also plays a major role in retinal neurotoxicity. Importantly, in experimental models of glaucoma, gene-targeted mice that express only full-length FasL exhibit accelerated death of RGCs and loss of nerve fibers. By contrast, FasL-deficiency, or forced expression of soluble FasL protected RGCs from TNF-triggered cell death. Intriguingly, microglial cells appear to be the FasL cytotoxic population. These data identify FasL as a critical effector molecule and potential therapeutic target in glaucoma.

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