

Identification of retinal ganglion cell neuroprotection conferred by platelet-derived growth factor through analysis of the mesenchymal stem cell secretome

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The development of neuroprotective strategies to attenuate retinal ganglion cell death could lead to novel therapies for chronic optic neuropathies such as glaucoma. Intravitreal transplantation of mesenchymal stem cells slows retinal ganglion cell death in models of optic nerve injury, but the mechanism of action remains unclear. Here we characterized the neuroprotective effects of mesenchymal stem cells and mesenchymal stem cell-derived factors in organotypic retinal explant culture and an *in vivo* model of ocular hypertensive glaucoma.

Co-culture of rat and human bone marrow-derived mesenchymal stem cells with retinal explants increased retinal ganglion cell survival, after 7 days *ex vivo*, by ~2-fold and was associated with reduced apoptosis and increased nerve fibre layer and inner plexiform layer thicknesses. These effects were not demonstrated by co-culture with human or mouse fibroblasts. Conditioned media from mesenchymal stem cells conferred neuroprotection, suggesting that the neuroprotection is mediated, at least partly, by secreted factors.

We compared the concentrations of 29 factors in human mesenchymal stem cell and fibroblast conditioned media, and identified 11 enriched in the mesenchymal stem cell secretome. Treatment of retinal explants with a cocktail of these factors conferred retinal ganglion cell neuroprotection, with factors from the platelet-derived growth factor family being the most potent. Blockade of platelet-derived growth factor signalling with neutralizing antibody or with small molecule inhibitors of platelet-derived growth factor receptor kinase or downstream phosphatidylinositol 3 kinase eliminated retinal ganglion cell neuroprotection conferred by mesenchymal stem cell co-culture. Intravitreal injection of platelet-derived growth factor -AA or -AB led to profound optic nerve neuroprotection *in vivo* following experimental induction of elevated intraocular pressure.

These data demonstrate that mesenchymal stem cells secrete a number of neuroprotective proteins and suggest that platelet-derived growth factor secretion in particular may play an important role in mesenchymal stem cell-mediated retinal ganglion cell neuroprotection. Furthermore, platelet-derived growth factor may represent an independent target for achieving retinal ganglion cell neuroprotection.

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