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Mead, Ben; Scheven, Ben

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Tamoxifen and Src kinase inhibitors as neuroprotective/neuroregenerative drugs after spinal cord injury

Iris K. Salgado, Aranza I. Torrado, Jose M. Santiago, Jorge D. Miranda

KEYWORDS: tamoxifen; Src kinase; PP2; trauma; regeneration; neuroprotection

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Mesenchymal stem cell therapy for retinal ganglion cell neuroprotection and axon regeneration

Retinal ganglion cells (RGCs) are responsible for propagating signals derived from visual stimuli in the eye to the brain, along their axons within the optic nerve to the superior colliculus, lateral geniculate nucleus and visual cortex of the brain. Damage to the optic nerve either through trauma, such as head injury, or degenerative disease, such as glaucoma causes irreversible loss of function through degeneration of non-regenerating RGC axons and death of irreplaceable RGCs, ultimately leading to blindness (Berry et al., 2008). The degeneration of RGCs and their axons is due to the loss of the necessary source of retrogradely transported neurotrophic factors (NTFs) being hindered by axonal injury. NTFs are survival factors for neurons and play a pivotal part in axon regeneration. Stem cells particularly mesenchymal stem cells (MSCs) have been shown to possess a natural intrinsic capacity for paracrine support, releasing multiple signalling molecules including NTFs. By transplanting MSCs into the vitreous, they are positioned adjacent to the injured retina to provide paracrine-mediated therapy for the retinal neuronal cells (Johnson et al., 2010a; Mead et al., 2013). Additionally, MSCs may be pre-differentiated into supportive glial-like cells, such as Schwann cells, which could further increase their potential for paracrine support of injured neurons (Martens et al., 2013). Thus, MSCs have received considerable attention as a new cellular therapy for both traumatic and degenerative eye disease, acting as an alternative source of NTFs, protecting injured RGCs and promoting regeneration of their axons (Figure 1).

Bone marrow mesenchymal stem cells: Bone marrow mesenchymal stem cells (BMSCs) were the first MSCs to gather interest as a cellular therapy for ocular disease. Following transplantation into the vitreous of a rat model of glaucoma, BMSCs increased the number of surviving RGCs by 10–20% (Yu et al., 2006; Johnson et al., 2010a). In a model of traumatic optic nerve injury, BMSCs increased the survival of RGCs by 15–20% 8–28 days after transection/crush of the optic nerve (Levkovitch-Verbin et al., 2010; Mead et al., 2013; Mesentier-Louro et al., 2014) and increased the number of regenerating axons found at distances 100–1,200 µm distal to the lesion site by 2-fold compared to control animals receiving dead cells (Mead et al., 2013; Mesentier-Louro et al., 2014). In both models, the BMSCs survived but showed no sign of differentiating into neuronal or glial phenotypes, thus leading to the conclusion that the neuroprotective effects elicited were through paracrine-mediated effects, either direct signalling between the grafted stem cells and the injured RGCs, or activation of retinal glia by the stem cells and glia-mediated neuroprotection/axonogenesis.

Dental pulp stem cells: We are interested in exploring the use of dental pulp stem cells (DPSCs) as an alternative source of stem cells for cellular therapy for the eye (Mead et al., 2013, 2014). DPSCs are neural crest-derived cells that can be isolated from adult teeth, an easily accessible source. Previous PCR-based gene expression studies suggested that, like BMSCs, DPSCs secrete multiple NTFs. In our most recent study using an in vitro co-culture system using axotomised RGC, we compared human-derived DPSCs, BMSCs and adipose-differentiated mesenchymal stem cells (ADSCs) for their potential to protect and regenerate injured RGCs (Mead et al., 2014). Like BMSCs and DPSCs, ADSCs secrete multiple different NTFs; however, their efficacy as a treatment for the eye is unknown. We cultured human-derived MSCs with injured rat retinal cells and assessed their neuroprotective and neuritogenic potential, and the role of specific NTFs including platelet-derived growth factor (PDGF) which was recognised as an important BMSC-derived factor for RGC neuroprotection (Johnson et al., 2013). In co-culture, we administered a variety of different Fc-fusion protein inhibitors to selectively block particular receptors and assess the changes in neuroprotective and neuritogenic effects elicited by the MSCs. This study highlighted several important points: firstly, human-derived DPSCs were the most neuroprotective and neuritogenic, followed by BMSCs and ADSCs, respectively; secondly, a variety of NTFs were identified to play a significant role in the neuroprotection/neuritogenesis seen, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), as well as other NTFs such as glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF) and PDGF-AA/AB/BB; thirdly, the neuritogenic properties of the MSCs were strongly inhibited by Fc-TrkAr, suggesting NGF plays an important role in MSC-mediated axon regeneration. Finally, using Fc-PDGF/Br inhibitors, our study underscored the important role of DPSC/MSC-derived PDGF-AA and PDGF-AB/BB in retinal neuroprotection confirming a previous study using BMSCs (Johnson et al., 2013). We substantiated our findings using ELISA analyses on conditioned media from MSCs, confirming the secretion of NTFs by the MSCs with significantly higher quantities from DPSCs (Mead et al., 2014). We also performed a PCR array on the MSCs which indicated a diverse NTF profile of the three MSC populations. The distinct NTF profiles of DPSCs, BMSCs and ADSCs underlined the fact that the source of MSC is critical for determining the effectiveness of a planned cellular therapy. The PCR array data also revealed a previously unconsidered, and relatively unknown, factor, VGF-neuropeptide, which was expressed at considerably higher titres in DPSCs than BMSCs or ADSCs. At the time of our studies, very little was known about the neuroprotective/neuroregenerative properties of VGF. Thus, we ventured to investigate the...
Mead et al., 2013). This remarkable ability of DPSCs/after intravitreal transplantation compared with BMSCs found at distances 100–1,200 µm distal to the lesion site ther 2-fold increase in the number of regenerating axons a significantly greater increase in RGC survival and a fur -
el of optic nerve/RGC injury whereby DPSCs promoted

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mary cells that DPSCs were more potent in their
MSCs corroborate our previous findings using rat pri-
trophic molecules may be residing in the cocktail of the
neuroprotection of RGCs (Mesentier-Louro et al., 2014),
demonstrated importance of FGF-2 in BMSC-mediated

Effects of the recombinant VGF-neuropeptide on injured retinal cultures and elucidated that this new factor pre-
sented a potent neuroprotective effect (Mead et al., 2014). Considering this novel finding as well as the recently demonstrated importance of FGF-2 in BMSC-mediated neuroprotection of RGCs (Mesentier-Louro et al., 2014), it is very plausible that other neuroprotective/axogenic trophic molecules may be residing in the cocktail of the MSC secretome. Our study using primary human-derived MSCs corroborate our previous findings using rat primary cells that DPSCs were more potent in their in vitro RGC neuroprotection and RGC neurotogenisis which corresponded with their secretion of significantly higher levels of NGF, BDNF and NT-3 than BMSCs (Mesentier-Louro et al., 2013). DPSCs were also more effective in an in vitro model of optic nerve/RGC injury whereby DPSCs promoted a significantly greater increase in RGC survival and a fur-

Further studies are warranted to clarify the most suitable stem cell injection site for retinal neural therapy.

Conclusions: Although we have performed an in depth comparison of three common human-derived MSC types and identified DPSCs as the most efficacious cell type for RGC neuroprotection and axon regeneration, further studies are required to confirm the relative (pre)clinical ef-

Engraftment of stem cells in the retina: One interesting observation is the surprising ability for MSCs to survive in vivo when transplanted in the eye, with multiple stud-

Figure 1 Schematic diagram demonstrating the effects of glaucoma and traumatic optic neuropathy on the eye and the potential of mesenchymal stem cells as a therapy.
the safety of BMSCs for retinal and optic nerve damage (www.clinicaltrials.gov/show/NCT01920867). Based on our recent findings, we propose DPSCs as a novel and advantageous MSC type for retinal neuroprotection and repair (Mead et al., 2013, 2014).

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Ben Mead*, Ben A. Scheven
Neurotrauma Research Group, Neurobiology Section, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, B15 2TT, United Kingdom (Mead B)
School of Dentistry, University of Birmingham, B4 6NN, United Kingdom (Mead B, Scheven BA)

*Correspondence to: Ben Mead, Ph.D., BXM813@bham.ac.uk.
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