LETTER TO THE EDITOR

Reply: Platelet-derived growth factor-BB may be involved in mesenchymal stem cell secretome-induced neuroprotection of retinal ganglion cells

Thomas V. Johnson,1 Keith R. Martin2 and Stanislav I. Tomarev3

1 Johns Hopkins School of Medicine, 1830 Monument Street, Suite 2-300, Baltimore, Maryland, 21205, USA
2 John van Geest Centre for Brain Repair, University of Cambridge, E.D. Adrian Building, Forvie Site, Robinson Way, Cambridge, UK
3 Section of Retinal Ganglion Cell Biology, Laboratory of Retinal Cell and Molecular Biology, National Eye Institute, National Institutes of Health, 6 Center Drive, MSC 0606, Building 6, Room 212, Bethesda, Maryland, USA

Correspondence to: Thomas V Johnson, PhD, Johns Hopkins School of Medicine, 1830 Monument Street, Suite 2-300, Baltimore, Maryland, 21205, USA
E-mail: tvjohnson@jhmi.edu

Sir, We are grateful for the opportunity to respond to the correspondence from Dr He, and we thank the author for his interest in our recent article, which demonstrated that platelet-derived growth factor (PDGF) is secreted by bone marrow-derived mesenchymal stem cells (MSCs) and confers neuroprotection to retinal ganglion cells in organotypic retinal explant culture and in an in vivo model of ocular hypertensive glaucoma (Johnson et al., 2013). Based on our previously reported observation that intravitreal MSC transplantation confers optic nerve neuroprotection (Johnson et al., 2010), we recently analysed the human MSC secretome and compared it to that of human fibroblasts using xMAP antibody-based arrays. As Dr He noted, we demonstrated that PDGF-AA secretion from MSCs was >500-fold greater than from fibroblasts, and that PDGF-AB/BB secretion was >120-fold greater. It should be noted that the analysis could not distinguish between the AB and BB isoforms of PDGF in cell-conditioned media, and therefore the relative levels at which MSCs secrete these isoforms remains to be determined. In addition, we identified nine other proteins with potential neuroprotective properties that were secreted at significantly higher levels by MSCs, and went on to assay their neuroprotective properties using organotypic retinal explant culture.

Because our analysis was intentionally broad and included growth factors and cytokines from many different molecular families, we chose to limit our investigation of PDGF specifically to two isoforms: AA which binds homodimeric PDGF-receptor (PDGFR)-αα exclusively and AB which binds both homodimeric PDGFR-αα and heterodimeric PDGFR-αβ (Chen et al., 2013). We reasoned that assaying the relative neuroprotective effects of these two isoforms could provide insight into the relative importance of PDGFR-αα versus PDGFR-αβ signalling in optic nerve neuroprotection. Our results suggested that activation of PDGFR-αα with PDGF-AA was extremely protective both in vitro and in vivo, and that the combined activation of PDGFR-αα and PDGFR-αβ with PDGF-AB or a combination of PDGF-AA and -AB was just as protective, but did not result in significantly greater cell or axonal survival. Nonetheless, it should be noted that the level of RGC cell body and axonal survival we observed with PDGF-AA treatment using these assays was ~100%, possibly resulting in a ceiling effect that obscured any additional protection that could have been demonstrated by alternative receptor isoform activation. Therefore, although our data clearly demonstrate a strong pro-survival effect on retinal ganglion cells conferred by PDGFR-αα activation via PDGF-AA treatment, elucidating the effects of PDGFR-αβ or -ββ activation in retinal ganglion cells will require additional experimentation. Potentially, experiments using PDGF-DD, which binds PDGFR-ββ much more specifically, could provide additional insights.

PDGF-BB is a more promiscuous isoform, binding both PDGFR-αα and -ββ dimers as well as the αβ heterodimer. Because of the more complex nature of its binding properties, we felt that further investigation of this PDGF isoform was beyond the scope of our initial investigation. However, we agree with Dr He that additional experiments to clarify the relative importance of PDGF receptor isoforms in retinal ganglion cell neuroprotection are warranted. As we and Dr He have noted, there is evidence that both the...
α and β isoforms of PDGFR are expressed in the retina (Biswas et al., 2008) and may play a role in neuronal death and survival (Mekada et al., 1998; Egawa-Tsuzuki et al., 2004; Ishii et al., 2006; Tang et al., 2010; Kanamoto et al., 2011; Johnson et al., 2013). Although our work has helped to identify the PDGF receptor and its downstream pathways as potential targets for neuroprotective strategies to treat glaucoma and other optic nerve diseases, additional data are clearly required to clarify the exact mechanisms underlying PDGF-mediated neuroprotection and the most appropriate translational methods to achieve it.

References