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EDITORIAL

Broadening our focus in the search for cell transplantation-based glaucoma therapies

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Over the past 15 years, the search for novel glaucoma therapies has progressively broadened in scope. Although intraocular pressure reduction remains the only intervention clinically proven to slow vision loss,[1,2] adjunctive treatments capable of protecting retinal ganglion cells (RGCs) and their axons through intraocular pressure-independent mechanisms have become a focus of much research. Promising neuroprotective strategies for glaucoma include modulation of neurotrophic signalling, oxidative stress, inflammation, and other processes implicated in the pathogenesis of the disease.

Concomitantly, progress in stem cell biology has raised hopes that cell transplantation strategies may be useful in treating many degenerative diseases, including glaucoma. Although enthusiasm initially grew from hopes of optic nerve regeneration,[3] studies to date suggest that RGC replacement will remain a major challenge. Perhaps more promising in the short-term is the potential for stem cell transplantation to confer neuroprotection to host tissues. Research is continuously expanding our understanding of therapeutically relevant properties possessed by stem cells, as well as other cell types. We suggest that the development of cell transplantation therapies for glaucoma could be advanced by widening our consideration of how these treatments could work and which cells could be used.

Broadening the focus on mechanisms of action

Using transplantation to selectively replace cells lost in disease is an obvious biomedical application of pluripotent cell technology. Indeed, this objective stimulated the earliest cell transplantation experiments in the central nervous system (CNS). Post-transplant improvements in neuronal survival and functional recovery following CNS injury and disease were initially attributed to neuronal replacement. Subsequent analyses, however, demonstrated that more subtle effects of stem cell transplantation probably accounted for a significant proportion of the treatment benefit. Such neuroprotection of host tissues by transplanted cells is sometimes referred to as a bystander effect.[4] The discovery of therapeutic mechanisms of action other than cell replacement has driven an important expansion of the possible applications of stem cell transplantation to many areas of medicine.

So far, many attempts to develop neuroprotective cell-based therapies for glaucoma have focused on a commonly cited hypothesis that grafted cells protect host tissues by secreting neurotrophic signalling molecules.[5–8] Although trophic factor secretion is undoubtedly important in some contexts, other factors may be equally or more critical in other situations, and should be explored. For instance, some types of stem cells possess an array of immunomodulatory properties that protect neurons during inflammatory neurodegeneration;[4] such mechanisms of neuroprotection may be relevant to glaucoma.[9] Cellular damage induced by reactive oxygen species and/or nitric oxide has also been implicated in the pathophysiology of glaucoma[10,11] and certain stem cells appear able to confer protection against oxidative stress.[12–14] Other pathophysiological mechanisms involved in glaucoma have been postulated including impaired blood flow/hypoxia, excitotoxicity, and altered calcium homeostasis; these might

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also be ameliorated by transplantation of cells with appropriate beneficial properties. Although investigations continue to determine the extent to which particular pathways contribute to RGC death in glaucoma, it is important to remember that stem cell transplantation could also attenuate RGC degeneration through currently unappreciated mechanisms.

Using cell transplantation to achieve neuroprotection has potential benefits over traditional pharmacological therapy as stem cells could potentially deliver protective factors locally (thereby circumventing bioavailability issues), deliver factors for a prolonged period of time following a single administration, and function through a synergistic combination of neuroprotective mechanisms (eg, by secreting neurotrophic factors and antioxidant molecules).

Broadening our focus on cell sources

Given that the potential biomedical applications of cell transplantation are expanding beyond the goal of cell replacement, broadening our consideration of cell sources for glaucoma therapies is also warranted. Stem and progenitor cells were initially the focus of investigation because of their ability to differentiate into mature cellular phenotypes (RGCs, for instance) and their capacity to replicate, generating sufficient numbers of cells for clinical therapy. However, if research confirms that grafted cells can effectively protect host tissue through neuroprotective mechanisms, then one need not limit cell source consideration to stem/progenitor cells; the pool of potential cell sources may be expanded to include cell classes that possess neuroprotective properties without necessarily being pluripotent (glial or immune cells, for instance). In fact, exploring alternate cell types for transplantation therapy may shed light on previously unappreciated mechanisms of RGC neuroprotection.

Neuroprotection need not even be an intrinsic characteristic of the cell graft, since at least a subset of protective properties might be amenable to induction, for example by gene transfer. Therefore, one might consider a transplanted cell to be simply a long-lived, locally situated delivery vehicle for biologically-derived therapeutic factors. Rather than focus on stem cells, more readily available cells such as fibroblasts could be altered to secrete neurotrophic factors, anti-inflammatory cytokines, and/or antioxidants. Indeed, one could potentially engineer neuroprotective cells for transplantation and deliver them to the eye inside a semi-permeable encapsulation device. This would facilitate precise localisation of the transplant away from the visual axis and permit straightforward removal should an adverse event occur, while providing constant delivery of protective factors from the graft. Such an approach is already being trialled for photoreceptor degeneration[15] and similar approaches may be considered for glaucoma.

Much work is needed to determine which neuroprotective approaches will be both applicable to glaucoma and feasible to target through cell transplantation. However, it appears to us that the full range of potential applications for therapeutic cell transplantation in glaucoma remains to be appreciated. Broadening our focus in the development of new cell transplantation-based therapies for glaucoma, with respect to both mechanism of action and source of cellular material, may yield significant new advances capable of effective, long-term protection of RGCs and visual function.

Conflict of interest

The authors declare no conflict of interest.

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