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REVIEW

Stem cell treatment of degenerative eye disease☆

Ben Mead[a,b,*], Martin Berry[a], Ann Logan[a], Robert A.H. Scott[a], Wendy Leadbeater[a,1], Ben A. Scheven[b,1]

[a] *Neurotrauma Research Group, Neurobiology Section, School of Clinical and Experimental Medicine, University of Birmingham, B15 2TT, UK*
[b] *School of Dentistry, University of Birmingham, B4 6NN, UK*

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Abstract
Stem cell therapies are being explored extensively as treatments for degenerative eye disease, either for replacing lost neurons, restoring neural circuits or, based on more recent evidence, as paracrine-mediated therapies in which stem cell-derived trophic factors protect compromised endogenous retinal neurons from death and induce the growth of new connections. Retinal progenitor phenotypes induced from embryonic stem cells/induced pluripotent stem cells (ESCs/iPSCs) and endogenous retinal stem cells may replace lost photoreceptors and retinal pigment epithelial (RPE) cells and restore vision in the diseased eye, whereas treatment of injured retinal ganglion cells (RGCs) has so far been reliant on mesenchymal stem cells (MSC). Here, we review the properties of non-retinal-derived adult stem cells, in particular neural stem cells (NSCs), MSC derived from bone marrow (BMSC), adipose tissues (ADSC) and dental pulp (DPSC), together with ESC/iPSC and discuss and compare their potential advantages as therapies designed to provide trophic support, repair and replacement of retinal neurons, RPE and glia in degenerative retinal diseases. We conclude that ESCs/iPSCs have the potential to replace lost retinal cells, whereas MSC may be a useful source of paracrine factors that protect RGC and stimulate regeneration of their axons in the optic nerve in degenerate eye disease. NSC may have potential as both a source of replacement cells and also as mediators of paracrine treatment.

Abbreviations: ADSCs, adipose-derived stem cells; AMD, age-related macular degeneration; BDNF, brain-derived neurotrophic factor; BMSCs, bone marrow-derived stem cells; CNS, central nervous system; CNTF, ciliary neurotrophic factor; DPSC, dental pulp stem cells; EGF, epidermal growth factor; ERG, electroretinogram; ESCs, embryonic stem cells; FGF, fibroblast growth factor; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; iPSCs, induced pluripotent stem cells; *ivit*, intravitreal; MSC, mesenchymal stem cells; mTOR, mammalian target of rapamycin; NGF, nerve growth factor; NSCs, neural stem cells; NT-3, neurotrophin-3; NTFs, neurotrophic factors; ONL, outer nuclear layer; RCS, Royal College of Surgeons rats; RGC, retinal ganglion cell; RPE, retinal pigment epithelial cells; SCI, spinal cord injury; TBI, traumatic brain injury; TrK, tropomyosin related kinase; VEGF, vascular endothelial growth factor.

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* Corresponding author at: Neurotrauma Research Group, Neurobiology Section, School of Clinical and Experimental Medicine, University of Birmingham, B15 2TT, UK.
E-mail address: BXM813@bham.ac.uk (B. Mead).
[1] Contributed equally and were joint senior authors.

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Introduction

The loss of retinal neurons, their connections and supporting glia in ocular degenerative diseases causes permanent blindness, principally because lost photoreceptors and retinal ganglion cells (RGCs) are not replaced and RGC axons fail to regenerate (Berry et al., 2008). Clinically, there are neither neuroprotective nor axogenic therapies available that restore lost visual system connectivity in retinal degenerative disease and translatable techniques for the replacement of lost RGC and photoreceptors are in their infancy. The retina is classified as central nervous system (CNS) tissue and the characteristics of its regenerative response are shared by other CNS tissues, including the brain and spinal cord.

Stem cell treatments developed as therapies for retinal degeneration fall into two broad categories: stem cells from (1), sources exogenous to the retina including mesenchymal stem cells (MSC) neural stem cells (NSCs) and embryonic/induced pluripotent stem cells (ESCs/iPSCs); and (2), endogenous retinal stem cells such as Müller glia (Ooto et al., 2004; Reichenbach and Bringmann, 2013), ciliary epithelia-derived stem cells (Ahmad et al., 2000; Tropepe et al., 2000) and retinal pigment epithelial (RPE) stem cells.

Potential non-retinal-derived adult stem cell based strategies being developed to treat retinal degeneration include NSC (McGill et al., 2012; Lu et al., 2013) and MSC derived from either bone marrow (BMSC) (Yu et al., 2006; Johnson et al., 2010; Levkovitch-Verbin et al., 2010), adipose tissues (ADSC) (Tsuruma et al., 2014) or dental pulp (DPSC) (Mead et al., 2013). MSC predominantly provide trophic support for the neuroprotection and axon regeneration of damaged retinal cells either directly through the secretion of neurotrophic factors (NTFs) (Johnson et al., 2010; Johnson et al., 2013; Mead et al., 2013) or possibly indirectly after stimulation of endogenous retinal cells (Lee et al., 2012) which, when activated, could provide additional paracrine support and/or effect cell replacement. There is no evidence that ESCs/iPSCs provide substantial paracrine support, but they do seem to be able to replace degenerating photoreceptors and RPE cells (Carr et al., 2009b; Lamba et al., 2009). NSCs directly differentiate into neural and glial phenotypes after transplantation into spinal cord injury (SCI) and traumatic brain injury (TBI) sites (Jeong et al., 2003; Lu et al., 2012). They also secrete trophic factors (Lu et al., 2003) and, although limited work has been performed in the eye with NSC, may have potential for both the neuroprotection and replacement of retinal neurons, including RGC. The differential efficiency of NSC/MSC/ESC/iPSC to perform these disparate tasks is the key to identifying the phenotype most fitted to provide the optimal safe therapy for retinal disease.

Of the endogenous retinal stem cells, Müller glia have been induced to dedifferentiate into retinal progenitors which can then transform into multiple retinal phenotypes including photoreceptors in the photoreceptor-damaged eye (Osakada et al., 2007; Liu et al., 2013). Ciliary epithelial-derived stem cells are self-renewing, multipotential retinal progenitor cells found in the pigmented ciliary epithelium of the retina (Xu et al., 2007), some of which differentiate in vitro into rhodopsin^{+} photoreceptors (Ballios et al., 2012; Clarke et al., 2012; Del Debbio et al., 2013). The RPE layer generates new retina in some animals (Fischer, 2005) and, in humans, contains a small population of stem cells that can mature into new RPE cells as well as cells with a neuronal phenotype (Salero et al., 2012). Whilst manipulation (Yu et al., 2014) and transplantation (Chacko et al., 2003; Canola et al., 2007) of endogenous retinal stem cells have the potential to treat retinal degeneration, their mechanism of action is largely restricted to RPE and