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Cellular strategies for retinal repair by photoreceptor replacement

Sujatha A. Jayakody [a, 1], Anai Gonzalez-Cordero [a, 1], Robin R. Ali [a, b, 1], Rachael A. Pearson [a, *, 1]

[a] Gene and Cell Therapy Group, Department of Genetics, UCL Institute of Ophthalmology, 11-43 Bath St, London EC1V 9EL, UK
[b] NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, City Road, London EC1V 2PD, UK

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ABSTRACT

Loss of photoreceptors due to retinal degeneration is a major cause of blindness in the developed world. While no effective treatment is currently available, cell replacement therapy, using pluripotent stem cell-derived photoreceptor precursor cells, may be a feasible future treatment. Recent reports have demonstrated rescue of visual function following the transplantation of immature photoreceptors and we have seen major advances in our ability to generate transplantation-competent donor cells from stem cell sources. Moreover, we are beginning to realise the possibilities of using endogenous populations of cells from within the retina itself to mediate retinal repair. Here, we present a review of our current understanding of endogenous repair mechanisms together with recent progress in the use of both ocular and pluripotent stem cells for the treatment of photoreceptor loss. We consider how our understanding of retinal development has underpinned many of the recent major advances in translation and moved us closer to the goal of restoring vision by cellular means.

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* Corresponding author. Department of Genetics, University College London Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK. Tel.: +44 (0) 2076084022.
E-mail address: rachael.pearson@ucl.ac.uk (R.A. Pearson).
URL: http://www.ucl.ac.uk/ioo/research/ali.htm

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1. Introduction

As visual animals, our sight is often regarded as our most important sense, with almost 30% of the sensory input to the brain originating from the retina (Dowling, 2012; Rodieck, 1998). It makes the loss of this sense a devastating one. Lower vertebrates possess an incredible intrinsic capacity for repair throughout their bodies, including complex neural structures like the retina. The mammalian neural retina, however, like many other regions of the central nervous system (CNS), lacks any significant regenerative potential to replace lost neurons after retinogenesis is complete. Consequently, any damage leading to the death of the light sensing photoreceptor cells or their support cells, either through injury or disease, typically leads to permanent visual impairment. The past decade has seen significant progress in our understanding of the underlying molecular mechanisms for a broad range of retinal diseases. Nonetheless, current clinical treatment options are limited to delaying the onset or decelerating the progress of the condition. To address this, extensive research effort has focussed on the development of novel therapeutic strategies. These include, amongst others, attempts to replace damaged cells by transplantation and strategies for the reactivation of endogenous stem cell populations to generate new photoreceptors. The regenerative ability of lower vertebrates has led researchers to investigate the mechanisms underlying these repair pathways to see if the same principles apply in mammals, including humans. Promisingly, a number of studies have demonstrated that some limited regenerative capacity remains in specific regions and cell types in the mammalian eye, including the ciliary epithelium (CE), retinal pigmented epithelium (RPE), iris and Müller glia cells. Endogenous repair is a very attractive strategy and a number of approaches have been employed to attempt to reactivate these cells *in vivo* (Fig. 1a). Thus far, the efficiency of reactivation and the potential of the newly generated cells are currently low and insufficient for the widespread repair of the mature mammalian eye following injury or disease. There remains much scope for improvement in this area, however. Moreover, *in vitro* culturing of these cells has yielded more hope that they might serve as a source of donor cells for cell replacement therapies (Fig. 1b). Effective cell replacement involves the identification of a renewable source of donor cells that have the ability to migrate into and correctly integrate within the recipient retina with high efficiency. Therefore, as well as focussing on ocular stem/progenitor cell niches, we also consider the different types of pluripotent stem cells available for transplantation purposes and our understanding regarding their potential to generate retinal cell types (Fig. 1c–d).

2. Retinal degeneration

Retinal degeneration is caused by the progressive loss of the sensory cells of the retina, the photoreceptors, and accounts for approximately 50% of all cases of blindness in the developed world (Bunce et al., 2010). Broadly, they fall into three forms: rod-degenerative forms, mixed rod/cone-degenerative forms or debris-associated forms (e.g. *mertk* defects and light damage). There are many causes of degeneration, primarily hereditary conditions and age related effects, but also diabetic retinopathy or retinopathy of prematurity.

Visual loss from inherited disease includes conditions such as retinitis pigmentosa (RP), choroideremia, Leber Congenital Amaurosis, Stargardt disease and Ushers disease and can arise from mutations in more than 200 different genes [see http://www.sph.uth.tmc.edu/Retnet/; (Hartong et al., 2006)]. As a result, the onset of hereditary disease and the speed of progression can be highly variable, depending upon the specific condition. This contrasts with age-related macular degeneration (AMD), which usually affects older adults (Minassian et al., 2011; Owen et al., 2012; Taylor, 2005). Currently, there are few effective treatments meaning that these conditions not only present a high socio-economic burden for patients and their families, but also for the healthcare system as a whole (Koberlein et al., 2013).

Of the retinal degenerative diseases, RP is perhaps the best characterised (Bird, 1995), with an incidence of 1 in 3500–4000 (Bunker et al., 1984). This group encompasses significant genetic and phenotypic heterogeneity. A wide variety of causes have been attributed; these include disruption of a number of genes that are involved in phototransduction, including the biosynthesis and folding of the photopigment molecule, Rhodopsin, as well as primary failure of the support cells within the retina, particularly the RPE. This heterogeneity means that RP has a highly variable clinical presentation and progression. However, the majority of patients initially experience problems in night vision, since the rod photoreceptors are typically damaged first, and a progressive loss of peripheral vision, leading to tunnel vision. In many cases, this can progress to include the central visual field and blindness (Hartong et al., 2006).