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Research review paper

Advances in repairing the degenerate retina by rod photoreceptor transplantation ☆

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ABSTRACT

Despite very different aetiologies, age-related macular degeneration (AMD) and most inherited retinal disorders culminate in the same final common pathway, loss of the light-sensitive photoreceptors. There are few clinical treatments and none can reverse the loss of vision. Photoreceptor replacement by transplantation is proposed as a broad treatment strategy applicable to all degenerations. The past decade has seen a number of landmark achievements in this field, which together provide strong justification for continuing investigation into photoreceptor replacement strategies. These include proof of principle for restoring vision by rod-photoreceptor transplantation in mice with congenital stationary night blindness and advances in stem cell biology, which have led to the generation of complete optic structures in vitro from embryonic stem cells. The latter represents enormous potential for generating suitable and renewable donor cells with which to achieve the former. However, there are still challenges presented by the degenerating recipient retinal environment that must be addressed as we move to translating these technologies towards clinical application.

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1. Introduction

Retinal degenerations leading to the loss of the light sensitive photoreceptors are a major cause of untreatable blindness in the UK. Inherited retinal dystrophies affect 1 in 3000 of the population, and Age-Related

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Macular Degeneration (AMD) affects 1 in 10 people over 60 years, a figure that is rising with an ageing population (Owen et al., 2012). Both conditions culminate in the same final common pathway, the loss of the light-sensing photoreceptors, which causes severe or complete loss of vision. In each case, there are few effective treatments and none of those currently available is able to replace lost photoreceptor cells and restore visual function. There is thus a need for new therapeutic approaches. Photoreceptors are afferent neurons and as such require no incoming connections. Moreover, they need only to make short, single synaptic connections to the remaining inner retinal circuitry to contribute to visual function. These features, arguably, make photoreceptor transplantation one of the most feasible types of Central Nervous System (CNS) repair and an excellent candidate for exploring regenerative neural stem cell therapies. The past decade has seen enormous progress in novel ocular therapies, including the first gene therapy (Bainbridge et al., 2008; Maguire et al., 2008) and retinal implant based (Chader et al., 2009) clinical trials for retinal disease, which have set the scene for pioneering new therapies for retinal disease. The success of gene therapy relies on the delivery of new functional genes to cells that lack such genes and is therefore dependent upon endogenous cell survival. In cases where the degenerative process has already led to cell death or in those conditions that are not amenable to gene therapy approaches, cell replacement therapies may offer a complementary approach. Given its accessibility, the eye has also been the model of choice for the study of neural development. As such, there is a wealth of knowledge regarding the intrinsic and extrinsic factors that regulate retinal histogenesis, knowledge that is now being employed to great effect in attempts to generate retinal cells from stem cells for transplantation (Eiraku et al., 2011; Lamba et al., 2009; Osakada et al., 2009). In this review, I will present a brief overview of the progress in photoreceptor replacement, in our ability to generate photoreceptors from stem cells and discuss some of the challenges that must be addressed as we begin to take this strategy towards clinical application.

2. Critique and discussion

2.1. Transplantation strategies

2.1.1. Retinal sheet transplantation

A central requirement of successful photoreceptor replacement therapy is the identification of an appropriate donor cell that has the ability to both migrate into the recipient retina following transplantation and differentiate into a fully functional, synaptically connected photoreceptor. Several transplantation strategies have been attempted, including the transplantation of whole sheets and microaggregates of developing neural retina and of dissociated adult hippocampal neural stem cells.

Work by Aramant and others have demonstrated that whole retinal sheets derived from either embryonic or neonatal retinae can survive and continue to differentiate after subretinal transplantation (Ghosh et al., 2004; Turner et al., 1988). More recently, they have shown that full-thickness retinal sheets can make limited connections with the recipient retina (Seiler et al., 2008). While there were some improvements in basic visual responses, for example light–dark discrimination, some authors have attributed this to the enhanced survival and function of endogenous photoreceptors by means of trophic factors released from the healthy transplanted tissue (Gouras and Tanabe, 2003). To date, retinal sheet transplantation in patients has shown some subjective visual improvement (Humayun et al., 2000; Radtke et al., 1999). A clinical study of retinitis pigmentosa (RP) and AMD patients who received foetal retinal sheet transplants (neural retina and retinal pigment epithelium, [RPE]), reported improvements in vision for 7 out of 10 patients, although the direct beneficial effects of the foetal retinal grafts are difficult to assess as all patients also received intraocular lens implants (Radtke et al., 2008). A further complication of full thickness retinal sheets is the inclusion of the inner retinal neurons that by definition are juxtaposed between the graft photoreceptors and the inner retinal neurons of the recipient retina. It remains to be determined to what degree this affects the processing of visual signals within the retina and beyond. An interesting related approach is the use of partial thickness grafts, encompassing the photoreceptor layer but omitting the inner retinal layer of the donor retina (Ghosh et al., 1999). Such a strategy might be of interest in severely degenerate retinas where the endogenous photoreceptor layer is completely absent although results to date have indicated only limited connectivity between the graft and the recipient retina.

2.1.2. Transplantation of dissociated cells

The limited integration between sheets and the recipient visual circuitry has prompted many groups to look at the transplantation of dissociated cell types. Given that the brain and the retina are both derived from the neuroectoderm and that immature neurons and progenitor cells are intrinsically capable of migrating and differentiating during neural development, numerous studies have investigated the potential of brain-derived neural stem/progenitor cells transplanted to the neural retina (Klassen et al., 2007; Mellough et al., 2007; Sakaguchi et al., 2004). However, transplantation of these cells into the adult retina has demonstrated only limited integration (Sakaguchi et al., 2005; Young et al., 2000). Moreover, these non-retinal sources of donor cells frequently fail to differentiate into mature retinal phenotypes, including photoreceptors, as assessed by immunohistochemistry (Young et al., 2000). More recent studies using tissue-restricted reporter genes to demonstrate retinal cell fate have confirmed that the integrated cells derived from such sources do not exhibit intrinsic features of mature retinal neurons (Sam et al., 2006).

To address this problem, progenitor cells isolated from embryonic retinas, which by definition possess the potential to differentiate into retinal neurons, have been tried; depending upon the conditions used to expand these cells in vitro prior to transplantation, these cells survive and differentiate into glial cells (Yang et al., 2002) and/or cells expressing retinal-specific markers, including some specific for photoreceptors (Qiu et al., 2005) upon transplantation. However, they also fail to become correctly integrated within the laminar structure of the neural retina, remaining instead at the site of transplantation. Greater success has been achieved when transplanting immature retinal cells into immature recipients, suggesting that the maturation state of the recipient may play a role in determining transplantation outcome: Murine progenitor cells transplanted into the eyes of neonatal Brazilian Opossums, which provide a foetal-like environment, survived and differentiated in vivo, although integrated cells were not found within the outer nuclear layer (ONL), where photoreceptors normally reside (Sakaguchi et al., 2004). Since the same donor cells failed to migrate into the retina of more mature recipients, it was suggested that the age of the host tissue had a key role in determining the fate of transplanted precursor cells and their ability to integrate into the circuitry of a non-autologous retina (Sakaguchi et al., 2003, 2004; Van Hoffelen et al., 2003).

By using postnatal donor cells from a transgenic mouse ubiquitously expressing Green Fluorescent Protein (GFP) and taking these cells from the peak of rod photoreceptor genesis and transplanting them into recipients of exactly the same developmental stage, MacLaren & Pearson et al., found that the transplanted cells migrated into the ONL (and no other layer) of the recipient retina and matured into morphologically normal photoreceptors. Moreover, these same cells could also integrate with equivalent efficiency into the non-neurogenic, adult retinal environment (MacLaren et al., 2006), as well as a number of models of retinal degeneration (Barber et al., 2013, 2008; MacLaren et al., 2006; Pearson et al., 2010) (but see further discussion). This indicated that transplantation success depended upon the developmental stage of the donor cell, rather than that of the recipient (Fig. 1).

Importantly, by using another transgenic model, in which GFP expression is under the control of the rod-specific transcription factor *Nrl*, which is first expressed shortly after terminal mitosis (Akimoto et al., 2006), the authors were able to demonstrate that these results

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