Chapter 12
Stem Cell Therapy for Retinal Disease Treatment: An Update

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12.1 Introduction

Retinal degenerative conditions lead to loss of visual function due the inability of a mammalian retina to repair or regenerate itself to a fully functional state. Use of stem cells to restore the anatomy and function of a degenerating retina, and thus vision, is an appealing concept. The most common of these conditions include age-related macular degeneration (AMD), retinitis pigmentosa (RP), and Stargardt disease (SD) (Zarbin 2016).

AMD affects 1.75 million persons in the USA and is the leading cause of blindness in people over the age of 55 years in the USA and Europe (Wong et al. 2014). Central vision is affected in AMD due to progressive degeneration of retinal pigment epithelium (RPE), the underlying choriocapillaris and the overlying photoreceptors (PRs) leading to atrophic patches of outer retina (GA, geographic atrophy) (Zarbin 2016). Central vision also can be affected by growth of abnormal blood vessels (CNV, choroidal neovascularization) under the RPE and retina. There is no proven therapy for GA, but there is effective drug therapy for CNV (Heier et al. 2012; Rosenfeld et al. 2006).

RP and SD are inherited retinal degenerations that cause vision loss in childhood or young adulthood (Parmeggiani 2011). In RP, several different mutations affecting the RPE or photoreceptors (PRs) lead to progressive degeneration of the outer retina throughout the eye causing loss of peripheral and central vision. RP affects 100,000 persons in the USA. SD has a prevalence of 1:10,000 births and is the most common inherited juvenile macular degeneration. Most cases are autosomal recessively

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transmitted and involve a mutation in PRs that causes progressive loss of central vision (Genead et al. 2009). There are no proven treatments for either RP or SD that might slow down the cell loss or restore lost vision.

While gene therapies and drug therapies are being explored as potential treatments for these conditions (Ashtari et al. 2015; Jacobson et al. 2015), none of them would be capable of restoring the PRs and RPE that are lost. Thus, in these cases, replacing the lost cells is an attractive concept that has been explored in animal and human studies. This article provides a brief overview of the use of stem cells in retinal degenerations.

12.2 Goals of Stem Cell Therapy: Rescue and/or Replacement

The goal of stem cell therapy is to either to "rescue" the surviving retinal cells (by providing the necessary support or generating neurotrophic agents) and/or to "replace" the cells that have degenerated. While the concept underlying replacement is straightforward, it became evident from early studies in animals that transplanting retinal cells has a positive effect on the survival of the adjacent cells as well as cells *at a distance* from the site of the transplant. For example, in Royal College of Surgeons (RCS) rats, a model for some forms of human RP, a mutation in transmembrane proto-oncogene tyrosine-protein kinase MER (MertK) in RPE causes poor phagocytosis of shed PR outer segments that subsequently causes degeneration of PRs (D'Cruz et al. 2000). Transplanting normal RPE had a positive effect not only in the immediate vicinity of the transplant site (by *replacing* the ineffective RPE) but also preserves PRs as far as away from the transplanted RPE as 1400 μm (Lund et al. 2001; Vollrath et al. 2001). This benefit was not due to migration of the transplanted cells and points to a trophic effect of the transplant. Indeed, RPE cells are known to produce several PR trophic factors (Kolomeyer and Zarbin 2014; Sun et al. 2015). The distinction may not simply be semantics. If only the outer segment (OS) of a PR has degenerated, for example, and rescue allows the OS to regenerate, then the goal of visual restoration is achieved in a less complicated way without the struggle of reconnecting a transplanted PR with the host retina (Sakai et al. 2003; Zarbin 2016).

12.3 RPE and PRs from Stem Cells

RPE can be harvested from human donor eyes, but they neither grow robustly, nor do they survive well in humans after transplantation. RPE derived from fetuses fare better, but ethical concerns as well as the limited ability to generate large numbers of genetically normal donor cells with serial passage prevent widespread evaluation and use. Stem cells, by nature of their virtually unlimited self-renewal and pluripotency, are a more attractive source for donor tissue.

Table 12.1 Sources of stem cells for retinal disease treatment

Cell type	Example of therapeutic cell type	Advantages	Disadvantages
Embryonic stem cell (ESC)	ESC-derived retinal pigment epithelium (RPE)	Pluripotency Grown relatively easily	Likely to be rejected if donor is allogneic
Adult stem cell	Bone-marrow derived stem cells Neural precursor cells	Multipotency Not rejected if transplanted into donor	Can be relatively hard to Harbors disease-causing genes of donor harvest
Induced pluripotent stem cell (iPSC)	iPSC derived RPE	Pluripotent Grown relatively easily Probably not rejected when injected into the donor	May retain epigenetic features of cell type of origin Harbors disease-causing genes of donor

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Embryonic stem cells (ESCs), derived from the inner cell mass of the blastocyst, can differentiate into cells of ectoderm, mesoderm, and endoderm (Reubinoff et al. 2000; Thomson et al. 1998). Further downstream in the differentiation of the retina is an intermediate cell type with relative reduced proliferative capacity, the multipotent retinal progenitor cell (RPC) (Luo et al. 2014; Marquardt 2003) that could also be a potential source of RPE and PRs. These cells have also been isolated from fetal and adult human eyes (Carter et al. 2007; Coles et al. 2004; Mayer et al. 2005; Yang et al. 2002; Blenkinsop et al. 2013).

Stem cells can be derived from adult tissues; multipotent stem cells have been found in various organs (Gage 2000; Weissman 2000), including the eye (Saini et al. 2016; Salero et al. 2012). In addition, stem cells isolated from a particular tissue can be induced to differentiate into an unrelated tissue. For example, neural stem cells can be induced to develop into muscle.

Pluripotent stem cells can also be generated by somatic nuclear transfer from an adult/fetal/neonatal cell into an unfertilized oocyte (Chung et al. 2014; Tachibana et al. 2013; Yamada et al. 2014), or by transfection of a differentiated adult cell with transcription factors that reactivate developmentally regulated genes, so called induced pluripotent stem cells (iPSCs) (Park et al. 2008; Takahashi et al. 2007) (see Table 12.1). Genetically matched cell lines might thus be generated for autologous transplants (Yabut and Bernstein 2011).

Protocols have been developed to derive retinal cells from ESCs (Osakada et al. 2008; Lamba et al. 2006; Yanai et al. 2016). These cells can rescue PRs in RCS rats (Schraermeyer et al. 2001) or migrate into rabbit retina and express PR markers such as S-opsin and rhodopsin (Amirpour et al. 2012). RPE cells also have been generated from ESCs (Gong et al. 2008; Idelson et al. 2009; Klimanskaya et al. 2004; Lund et al. 2006). These cells also rescue PRs in RCS rats (Lund et al. 2006) and express RPE characteristics including ion transport, resting membrane potential, transepithelial resistance, and visual pigment recycling (Bharti et al. 2011; Maeda et al. 2013).

Other potential sources have been explored. In situ RPE have been recently found to contain a small population of multipotent cells (RPE-ESC) that can be cultured (Saini et al. 2016; Salero et al. 2012) although they may not have the same expansion capability as ESC- or iPSC-derived RPE. Bone marrow-derived stem cells (mesenchymal stem cells) have also been used to generate RPE (Arnhold et al. 2006; Mathivanan et al. 2015). By using surface markers to select the stem cells that have the potential to differentiate into RPE and then co-culturing with mitomycin C-inactivated RPE cells, Mathivanan and coworkers showed that these cells exhibit some of RPE markers and are capable of rescuing PRs after transplantation into RCS rats (Mathivanan et al. 2015). The above two sources may have limitations due to the number of cells that can be derived from them and the lack of complete characterization of these cells.

Can stem cells be differentiated into fully functional RPE and PRs? As noted above, RPE cells that have been derived from ESCs and iPSCs need to exhibit proper ion transport, membrane potential, ability to phagocytose shed PR OSs, polarized vascular growth endothelial growth factor secretion (to maintain normal subjacent choriocapillaris anatomy), visual pigment recycling, and gene expression profiles similar to those of in situ healthy RPE. Expression of these features has varied from lab to lab. A thorough and comprehensive group of functional tests to ascertain the extent of stem cell-derived RPE differentiation has been proposed (Bharti et al. 2011). Using current manufacturing techniques, stem cell-derived RPE can perform the expected functions after transplantation into rodent models of retinal degeneration (Kamao et al. 2014; Maeda et al. 2013; Li et al. 2012; Tsai et al. 2015).

12.4 Experimental Studies and Challenges

Table 12.2 lists ongoing human stem cell trials for retinal degenerative diseases. Stem cells being used include iPSC-RPE, ESC-RPE, iPSC-neural precursor cells (NPCs), bone marrow-derived stem cells, and human central nervous system derived stem cells among others. It is too early to judge the outcome of these sources of tissue. A number of challenges remain that may hinder a successful outcome. Growth arrest due to rapid telomere shortening, chromosomal DNA damage, and increased cyclin-dependent kinase inhibitor 1 (p21) expression (Feng et al. 2010; Kokkinaki et al. 2011), for example, can limit the success of iPSC transplant survival and function.

12.4.1 Stem Cells for Human Transplantation

Generating adequate stem cells in an efficient, rapid, and safe manner would permit widespread use. Phenotypic instability or altered gene expression during serial passaging in culture, including up-regulation of oncogenes, might occur and mandate careful monitoring of the manufacturing process (Klimanskaya et al. 2004; Anguera et al. 2012; Shen et al. 2008).

Table 12.2 Current human cell therapy trials for retinal diseases

Disease (Clinicaltrials.gov Identifier)	Phase	Cell type transplanted	Center (PI)	Sponsor
AMD (NCT00874783)	Observational	iPSCs	Hadassah Medical Organization (Reubinoff)	Hadassah Medical Organization
AMD-GA (NCT02286089)	I/II	ESC-RPE	Hadassah Ein Kerem University Hospital (Hemo)	Cell Cure Neurosciences
AMD-GA (NCT02016508)	I/II	Bone marrow-derived SCs	Al-Azhar University (Safwat)	Al-Azhar University
AMD-GA (NCT02590692)	I/IIa	ESC-RPE on a polymeric substrate (CPCB-RPE1)	Retina Vitreous Associates Medical Group (Rahhal) USC Keck School of Medicine (Kashani)	Regenerative Patch Technologies
AMD-CNV (NCT01691261)	I	ESC-RPE on a polyester membrane	University College London (Pfizer)	Pfizer
AMD-GA or CNV (NCT02464956)	Observational	Autologous iPSC-RPE	Moorfields Eye Hospital	Moorfields Eye Hospital NHS Foundation Trust
AMD (NNCT01920867)	Interventional	Bone marrow-derived SCs	Retina Associates of South Florida (Weiss)	Retina Associates of South Florida
AMD-GA (NCT01736059)	I	Bone marrow-derived CD34+ SCs	University of California, Davis (Park)	University of California, Davis
AMD-CNV	Interventional	Autologous iPSC-RPE	Riken Institute for Developmental Biology (Takahashi)	Riken Institute for Developmental Biology

(continued)

Table 12.2 (continued)

Disease (Clinicaltrials.gov Identifier)	Phase	Cell type transplanted	Center (PI)	Sponsor
Stargardt disease (NCT01345006, NCT02445612, NCT01469832)	I/II	ESC-RPE (MA09-hRPE)	Jules Stein-UCLA (Schwartz) Wills Eye Hospital (Regillo) Bascom Palmer Eye Institute (Lam) Moorfields Eye Hospital (Bainbridge)	Ocata Therapeutics
AMD-GA (NCT01344993, NCT02563782, NCT02463344)	I/II	ESC-RPE (MA09-hRPE)	Jules Stein-UCLA (Schwartz) Wills Eye Hospital (Regillo) Mass. Eye and Ear Infirmary (Eliott) Bascom Palmer Eye Institute (Rosenfeld)	Ocata Therapeutics
AMD-GA (NCT01632527)	I/II	HuCNS-SC	Retina Foundation of the Southwest (Birch)	StemCells
AMD-GA (NCT01674829)	I/II	ESC-RPE (MA09-hRPE)	CHA Bundang Medical Center (Song)	CHA Bio and Diostech
Stargardt disease (NCT01625559)	I	ESC-RPE (MA09-hRPE)	CHA Bundang Medical Center (Song)	CHA Bio and Diostech
Myopic macular degeneration (NCT02122159)	I/II	ESC-RPE (MA09-hRPE)	Jules Stein-UCLA (Schwartz)	Ocata Therapeutics
AMD-GA (NCT01226628)	I	CNTO 2476 (umbilical tissue-derived cells)	Wills Eye Hospital (Ho)	Janssen Research and Development

Table 12.2 (continued)

Disease (Clinicaltrials.gov Identifier)	Phase	Cell type transplanted	Center (PI)	Sponsor
AMD-GA or CNV (NCT01518127)	I/II	Autologous bone marrow-derived SCs	University of Sao Paulo, Brazil (Siqueira)	University of Sao Paulo
RP and cone-rod dystrophy (NCT01068561)	I/II	Autologous bone marrow-derived SCs	University of Sao Paulo, Brazil (Siqueira)	University of Sao Paulo

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12.4.2 Cell Delivery

Various techniques have been used and are being explored to allow for an efficient and effective delivery of transplanted cells to the retina. The transplant cells may be injected into the vitreous (Park et al. 2015) or into the subretinal space (Schwartz et al. 2015; Li et al. 2012) as a cell suspension (intravitreous or subretinal delivery) (Diniz et al. 2013) or as a sheet of cells (subretinal delivery) (Kamao et al. 2014) with or without a biocompatible scaffold (Hsiung et al. 2015; Redenti et al. 2008; Tao et al. 2007; Tucker et al. 2010; Stanzel et al. 2014). Advantages of a cell suspension include ease of preparation and ease of delivery through a small retinotomy. However, there is little control of how transplanted cells reorganize in the subretinal space. The cells may form multilayers; they may not be polarized in the correct way; and the cells, especially RPE transplants, will need to re-attach to an abnormal Bruch's membrane surface. Cells sheets, on the other hand, allow for placement of properly polarized cells (e.g., apical villi of RPE facing PR OSs) that can start functioning immediately, and the scaffold that holds the cell sheets may allow for integration of growth factors or immunomodulatory factors to promote transplant survival and function. The scaffold may also confer some degree of protection against Bruch's membrane-induced cell death. Placement of cell sheets, however, requires a larger retinal opening that could potentially lead to egress of transplanted cells or retinal detachment after surgery.

Different potential scaffolds to support RPE sheet transplants are being explored (Kundu et al. 2014; Nazari et al. 2015). These include vitronectin-coated polyester membranes (Carr et al. 2013) and parylene C scaffolds manufactured using nanotechnology (Lu et al. 2012, 2014).

Transplants of PR sheets have consisted of either PR sheets, full thickness retinal sheets, or retina-RPE sheets (Assawachananont et al. 2014; Radtke et al. 2008;

Huang et al. 1998; Radtke et al. 1999). While the full thickness retina can still establish synaptic connections and restore visual responses in rats (Seiler et al. 2010), for example, whether patients would experience useful visual improvement given the altered anatomy of a "double" retina is not clear. How a suspension of PRs compares to a sheet of pure PRs is also not known.

12.4.3 Transplant Survival, Differentiation, and Integration

For transplantation to be successful, RPE must survive in the subretinal space, reattach to the underlying Bruch's membrane (the structure on which RPE normally reside), be polarized so that PR OSs can be phagocytosed by the apical villi, and establish an outer blood-retinal barrier (e.g., via tight junctions between adjacent RPE cells). PR transplants will need to survive, extend axons to form synapses with the host bipolar cells one side, and extend OSs towards the native RPE cells on the other side. Loss of PRs due to mutations or retinal detachment leads to subsequent synaptic rewiring between other interconnected retinal cells (Khodair et al. 2003; Lewis et al. 1998; Jones et al. 2003). In other words, a mere integration of the transplanted PRs with the downstream bipolar cells alone may not be sufficient for complete visual recovery due to synaptic rewiring of the retina that occurs once host PRs have degenerated.

Results from preclinical models of RP indicate that if one transplants suspensions of rod PRs into the subretinal space, the cells need to be of a specific developmental stage for the transplant to have the highest chance of success. Specifically, post-mitotic rod precursors that express the rod-specific transcription factor, Nrl, yet are morphologically immature, seem to give the best results (MacLaren et al. 2006; Pearson 2014; Pearson et al. 2012; Akimoto et al. 2006). In addition, with current techniques, it is important to transplant a large number of cells (~200,000) to achieve improved visual function. Wild-type rod PR precursors generated from fetal tissue and transplanted into rd1 mice (which lack phosphodiesterase-6-beta (Pde6b) and exhibit rapid rod PR death after birth) express Pde6b in an appropriately polarized fashion, exhibit abnormally short OSs, and support improved visual function (Singh et al. 2013). In the rd1 recipients, the host bipolar and Muller cells extend processes into the PR graft and appear to make synaptic contact with the donor PRs (Singh et al. 2013). Gonzalez-Cordero and co-workers harvested developing PRs from optic cups generated from ESCs in vitro and noted that best integration with host rd1 retina occurs when these PR precursors are still immature but committed to becoming PRs, which is quite similar to the results observed when using fetal tissue as the source of PR precursors (Gonzalez-Cordero et al. 2013). Host retinal anatomy can modulate the efficacy of PR transplantation. If the host retina has significant PR damage and abnormal anatomy, the transplanted PRs also tend to exhibit abnormal and limited synapse formation (Barber et al. 2013). Glial scarring limits integration in more advanced stages of retinal degeneration, and attenuating the glial barrier helps promote better integration in some types of retinal degeneration

(Pearson 2014; Barber et al. 2013; Pearson et al. 2010; Hippert et al. 2016). An additional barrier may be the external limiting membrane (ELM), which is formed by the junction of Muller cell apical processes and PR inner segments via adherens junctions. In one study, transient ELM disruption using alpha amino adipic acid improved PR precursor integration by ~100% (West et al. 2008; Pearson et al. 2010). Indeed, in retinal degenerations associated with ELM disruption, there is greater integration of transplanted PRs with host retina (Barber et al. 2013).

In principle, it should be easier to achieve clinically successful outcomes after RPE transplantation (for the purpose of "rescue") than after PR transplantation (for the purpose of "replacement") since RPE integrate with host PRs spontaneously. Thus, the only challenge for a successful RPE transplant, apart from the need to control immune surveillance, involves resurfacing an atrophic patch in the foveal area in AMD patients with GA. Transplanted RPE have been shown to survive and rescue PRs in numerous preclinical studies. However, human studies have not resulted in a comparable degree of success (Binder et al. 2007; Gullapalli et al. 2012). RPE survival has been shown to be poor when transplanted onto Bruch's membrane from aged human cadaver eyes or eyes with advanced AMD with GA (Sugino et al. 2011b; Gullapalli et al. 2005). In addition, human Bruch's membrane has been shown to undergo changes resulting from aging including thickening, advanced glycation end-product formation, lipid and protein deposition, and protein crosslinking (Zarbin 2004). As mentioned above, one way to address this issue would be to use scaffolds on which transplanted RPE could be delivered as a differentiated cell sheet in which the scaffold provides a surface conducive to cell survival and prevents contact of the transplant with subjacent host Bruch's membrane. Use of conditioned medium derived from bovine corneal endothelial cells has been shown to improve transplanted RPE survival on human cadaver eyes with GA (Sugino et al. 2011a) by altering cell behavior on this surface. Identification of molecules responsible for this effect might allow development of an adjunct that would improve transplanted RPE cell survival in AMD eyes, even when cell suspensions are used.

12.4.4 Immune Response

The subretinal space is an immune privileged site, i.e., allografts survive longer in this privileged site compared to a non-privileged site such as the subconjunctival space. Native neonatal RPE behaves as an immune privileged tissue, i.e., RPE resist rejection at heterotopic sites (Wenkel and Streilein 2000). Do stem cell-derived RPE behave as immune privileged tissue? ESCs and their derivatives have been shown to escape a host immune rejection for a long time (Yuan et al. 2007). This phenomenon may be due to low expression of human leukocyte antigen (HLA) class I molecules and no expression of class II molecules in their resting or differentiated state (Drukker et al. 2002). ESCs have also been shown to suppress T-cell proliferation (Li et al. 2004). iPSCs, on the other hand, appear to capable of inducing immune rejection (Sohn et al. 2015), even if autologous (Zhao et al. 2011).

Disruption of the blood-retinal barrier can be a significant factor in stimulating the immune response. For example, disruption of native RPE (e.g., using sodium iodate) results in loss of the immune privilege of the subretinal space. Preservation of the barrier diminishes the immune response (Lu et al. 2010). RPE transplants in rabbits require immune suppression for sustained cell survival, (Stanzel et al. 2014) but this result may be due to the merangiotic nature of rabbit retina (i.e., only a choroidal blood supply for most of the retina) (De Schaepdrijver et al. 1989). In contrast, human retina is holangiotic (i.e., the retinal and choroidal circulation provide blood flow to the retina). Activation of the innate immune system can lead to activation of the adaptive immune system, which mediates immune surveillance. As a result, it is important to use surgical techniques and devices that minimize disruption of the blood retinal barrier and that incite acute inflammation.

Microglial activation in the host retina has been attributed to failure of grafts to survive and integrate (Bull et al. 2008; Singhal et al. 2008). Suppression of microglial activation may improve transplant survival and integration (Xian and Huang 2015).

Postoperative immune suppression will likely be needed for RPE transplants, but elderly patients with AMD may not be able to tolerate extended periods of immune suppression (Tezel et al. 2007). Long-acting intravitreal steroid preparations may be of use. It is not clear that PR transplants will require long-term immune suppression as these cells exhibit very low MHC class II expression. However, if full thickness retina transplants are used or if impure PR preparations are used, then transplantation of microglia will probably activate a host immune response.

12.4.5 Tumor Formation

One of the important risks of stem cell transplants is development of tumors. When ESC-derived neural precursors were injected into the subretinal space of rhodopsin knockout mice, 50 % of the eyes developed tumors (teratomas) within 8 weeks (Arnhold et al. 2004). (These mice have a mutation resembling autosomal dominant RP.) When iPSC and ESC mouse lines were compared, there was high incidence of teratoma formation with both of them (Araki et al. 2013). There have been no reported tumor issues with patients with SD and AMD who have received ESC-derived RPE cells (Song et al. 2015; Schwartz et al. 2015). iPSC cell lines may be more prone to genetic instability due to the risk of insertional mutagenesis from use of viral vectors and use of oncogenic factors such as c-Myc during cell production. Use of non-integrating reprogramming methods in the production of iPSC cell lines might reduce the risk (Kang et al. 2015) by increasing genomic stability. Nonetheless, careful sustained monitoring will be needed.

12.5 Conclusion

The concept of transplanting healthy cells into diseased retina to restore vision is appealing. Significant progress has been made during the last 30 years. Preclinical testing has demonstrated the feasibility of cell-based therapy for the purpose of sight preservation as well as sight restoration. This research also has identified obstacles to success including graft survival and differentiation as well as immune rejection. Strides in stem cell research have allowed for expanding the field significantly. Early phase human trials using stem cell-derived donor tissue have also been promising. Continuing research in various aspects of transplantation- establishing cell lines without danger of tumor formation or immune rejection, refining surgical techniques and instruments, and identifying factors that promote cell survival, differentiation, and integration of the transplanted cells, should allow for rapid and continued progress in the field.

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