

Promises of stem cell therapy for retinal degenerative diseases

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Abstract With the development of stem cell technology, stem cell-based therapy for retinal degeneration has been proposed to restore the visual function. Many animal studies and some clinical trials have shown encouraging results of stem cell-based therapy in retinal degenerative diseases. While stem cell-based therapy is a promising strategy to replace damaged retinal cells and ultimately cure retinal degeneration, there are several important challenges which need to be overcome before stem cell technology can be applied widely in clinical settings. In this review, different types of donor cell origins used in retinal treatments, potential target cell types for therapy, methods of stem cell delivery to the eye, assessments of potential risks in stem cell therapy, as well as future developments of retinal stem cells therapy, will be discussed.

Keywords Retinal degenerative diseases · Stem cell therapy · Donor cells · Target cell types · Method of cell delivery · Potential risks · Clinical applications

The authors have full control of all primary data, and agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data upon request.

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Introduction

Retinal degeneration culminating in retinal cell loss is a major cause of permanent blindness in the world, leading to the loss of human resources and imposing a great financial burden of health care. Retinal degeneration can be found in the entire age spectrum. Epidemiologic studies have shown that retinitis pigmentosa (RP) affects predominantly the pediatric and young adult population [1], while diabetic retinopathy (DR) affects middle-aged adults [2], and age-related macular degeneration (AMD) affects the elderly.

Current therapeutic strategies for retinal degenerative diseases include pharmacological treatment, surgical intervention, and cell replacement. Pharmacological treatment is the commonest approach, but it is frequently ineffective for degenerative diseases such as RP. Surgical intervention such as autologous translocation of retinal pigment epithelium (RPE) have been tried for the treatment of neovascular AMD [3, 4], but outcomes are variable, and such surgical intervention is technically difficult. More importantly, this surgery is unable to regenerate damaged retinal. Poor renewability of retinal neurons has further limited the efficacies of the above therapies.

Recently, stem cell-based therapy for retinal degeneration has been proposed with the development of stem cell technology [5]. Stem cell-based therapy has been tested in animal models for several retinal degenerative diseases [6]. In 2010, the Food and Drug Administration (FDA) approved a phase I/II clinical trial using human embryonic stem cell (hESC)-derived RPE cells for the treatment of dry AMD. Transplantation of functional retinal cells or stem cells aims to restore vision by repopulating the damaged retina via rescuing retinal neurons from further degeneration. Although this is a milestone in clinical therapeutics, ethical controversies and risk of immune rejection have limited hESC-based

therapy in clinics. Despite the possibility of curing the degenerative process [7], there are still many obstacles before stem cell technology can be applied in daily practice. In this review, different types of donor cell origins used in retinal treatments, potential target cell types for therapy, method of delivery, assessments of potential risks in stem cell therapy, and also future developments will be discussed.

Donor cell origins

The success of stem cell therapy is highly dependent on the ability of donor cells to migrate into the desired location, to survive after transplantation, and to differentiate into retinal cells to restore retinal function. Recent researches have shown that several cell populations may be considered as potential sources. These include fetal stem cells, pluripotent stem cells (embryonic stem cells and induced pluripotent stem cells) and adult stem cells.

Fetal stem cells

Fetal stem cells are fetal retinal cells, at the exact developmental time when these cells are born and about to form intrinsic connections. Previous studies have shown that, before the formation of synaptic connections, retinal ganglion cells can regenerate after axotomy and navigate through the optic chiasm [8]. It has been proposed that immature photoreceptors might also have the capacity to reconnect themselves to the central neural system (CNS) after transplantation. Fetal retinal progenitor cells (RPCs) derived from a range of mammalian species, including rats [9, 10], pigs [11], and humans, [12] have been tried. It has been shown that rodent fetal RPCs are able to propagate extensively, expressing photoreceptor markers. Transplantation of fetal RPCs resulting in the survival and differentiation of the grafted tissue has been proven to be associated with behavioral benefits in retinal dystrophic recipients [13, 14]. Fetal neurons appear to show higher survival capacities than adult neurons [15]. For human fetal-derived retinal cells, Young [12] isolated proliferating human retinal progenitor cells (hRPCs) from 10th to 13rd week of gestation, and demonstrated that they could be expanded in tissue culture. However, their proliferating capacity was weak, and population declined quickly. Recently, Aftab et al. [15] have shown that donor tissues taken from 16th to 18th week of gestation give the longest in-vitro survival time, and the highest number of cells. After transplantation, these cells were integrated into the recipient retina, and differentiated into rhodopsin positive cells. This result supported the potential of hRPC transplantation for degenerative diseases. Nevertheless, ethical issues still exist, and the supply of such cells is still limited.

Embryonic stem cells and induced pluripotent stem cells

An alternative is to use embryonic stem cells and induced pluripotent stem cells (ESC/iPSC). ESCs/iPSCs have a great potential to differentiate into any of the 200 or more adult cell types. Hence ESC/iPSC provides potentially unlimited cell sources for the generation of retinal cells. In-vitro differentiation of ESC/iPSC into functional retinal cell types is achievable by defined step-wise protocols [16–19]. ESCs could be induced to differentiate into eye-like structures that contained cells with properties of crystalline lens, neural retina, and RPE [20]. Further studies have indicated that cells from these eye-like structures could be further differentiated into RGCs when transplanted into the vitreous of an injured adult mouse retina [21]. Recently, the success of defined differentiation of human ESC-derived RPE cells (hESC-RPE) has been reported [22]. Following transplantation in animal models, restoration of vision had been reported and no tumor formation was seen [19, 23]. In 2010, the FDA approved the first clinical trial using hESC-RPE for the treatment of dry AMD and Stargardt's disease (STGD) in humans. Hopefully results will be available in the near future. The main advantage over adult-derived RPE cell lines is the ability to produce differentiated RPE cells in vitro, which is less immunogenic.

Transplantation of hESC-derived RPE cells has proved to be a milestone in clinical therapeutics. Nevertheless, its use is still limited by ethical controversies and the risk of rejection. Induced pluripotent stem cells (iPSC) offer an alternative cellular source for patient-specific treatment without the risk of rejection and ethical problems [24, 25]. Nonetheless, clinical application of iPSCs is limited by the risks of proviral integrations and potential insertional mutagenesis during delivery of reprogrammed factors using virus. To overcome these issues, efforts toward the generation of "clinical grade" iPSC have been proposed. Recently, the reprogramming technologies in iPSC generation have been rapidly improved by the use of chemicals, plasmids, synthesized mRNAs, and direct protein delivery [26–29]. In the future, transplantation of photoreceptors with or without RPE cells derived from these sources provides enormous potential for treating retinal degenerations. Personalized treatment strategy is potentially possible with the use of iPSCs, assuming that the risks associated are minimized.

Adult stem cells

It is known that lower vertebrates, such as teleosts or amphibians, have the ability to regenerate new retinal neurons throughout life, from a region called the ciliary marginal zone (CMZ) [30, 31]. It was also thought that the adult mammalian ciliary body (CB) might harbor retinal stem cell. In 2000, two independent groups discovered that the

ciliary epithelium (CE) of the murine eye contains multipotent retinal stem cells [32, 33]. It was shown that single pigmented cells from the CE of mouse retina could clonally proliferate *in vitro* and form sphere colonies. These cells have the ability to be induced into retinal-specific cell types, including rod photoreceptors, bipolar neurons, and Müller glia.

Similar multipotent retinal stem cells were later identified in other mammalian species, including pigs and humans [34, 35]. These cells were proliferative, but to a lesser extent than fetal or ESC-derived retinal stem cells. When these cells were transplanted into adult mice, new photoreceptors were induced [35].

Another source of retinal stem cells was later discovered within the iris epithelium by Haruta and colleagues in 2001. The iris epithelium might harbor discrete heterogeneous populations of cells endowed with innate neural stem cell properties, including the ability to differentiate into retinal specific neurons [36, 37].

After the discovery of adult retina-specific stem cells, a number of laboratories have sought to expand numbers of such adult retina-specific stem cells and optimize sub-retinal differentiation. However, there are several obstacles to the use of such cells. Firstly, the percentage of actively proliferating cells in the CE is very few (<2%) [38]. Secondly, self-renewal and proliferation rates would decrease gradually with subsequent passages [35, 38]. Thirdly, there may be a risk of tumour formation, as reported by Djojotubroto [39] in a recent study. Furthermore, Gualdoni [40] found that the expansion of CE-derived cells quickly led to the loss of retinal progenitor cell markers and hence reduced the potential of photoreceptor differentiation. Further investigations are needed to delineate the intrinsic mechanisms governing adult stem cell self-renewal and differentiation, as well as genetic stability.

Other adult stem cells have also been reported to be capable of inducing retinal regeneration. These include neural progenitor cells (NPC) [41, 42], hematopoietic stem cells (hSC) [43], and mesenchymal stem cells (MSC) [44]. NPCs have been shown to promote the recovery from retinal injury and to express retinal phenotypic neurochemical markers [45]. However, reports have shown that NPC lacks the ability to differentiate into mature retinal neurons [46]. Furthermore, the shortage of adult NPC sources has further limited its application.

Autologous transplantation using hSC or MSCs has the advantage of reducing the risk of rejection and avoiding ethical controversies. Using retinal ischemia-reperfusion models, anatomical integration has been reported by intravitreal injection of hSCs [43, 47] and MSCs [48]. Animal studies have demonstrated that MSCs is capable of integrating into the ganglion cells and nerve fiber layers. Due to the fact that MSC derived from an elderly donor has

limited functions, MSC derived from human embryonic stem cells or iPSCs serves as an alternative source [49, 50].

Functional retinal differentiation from hSCs or MSCs is still highly debatable. More evidence has suggested that improvements with the use of adult hSCs or MSCs may actually be attributed to the secreted neurotrophic factors and anti-inflammatory cytokines *in situ*, instead of direct functional retinal differentiation [44, 51].

Retina-specific cell types can be derived from various cell sources. Different cell sources and important growth factors and chemical modulators used to promote retinal cell differentiation are summarized in Table 1.

Adult bone marrow stem cells

Cells of bone marrow origin have also been used for retinal regeneration. Bone marrow contains subsets of non-haematopoietic lineages, which are capable of multilineage differentiation into cells of non-haematopoietic capabilities. These include mesenchymal, endothelial, and very small embryonic/epiblast-like stem cells (VSEL). These cells proliferate and act in response to tissue injury or damage. Although most of these cells are organ-restricted, some appear to retain multipotential capacities [52]. In a mouse model, Li [53] showed that adult bone marrow-derived stem cells (BMSC) could be induced into RPE lineage *in vitro*. When infused back *in vivo*, these BMSC-derived RPE cells can home onto the focal areas of RPE damage, and form a monolayer on Bruch's membrane.

Potential target cell types for therapy

Retinal pigmented epithelial cells (RPE)

Retinal pigment epithelium is essential for the maintenance of neural retinal function. There is evidence suggesting that retinal degeneration can be treated with subretinal injections of RPE cells. Transplantation of RPE was first reported in the late 1980s [54, 55], on dystrophic Royal College of Surgeons (RCS) rats. These rats have defective RPE cells, which eventually lead to photoreceptor cell death. Since then, significant progress has been made regarding autologous RPE transplantation. Recent advances in stem cell culture and differentiation techniques have made possible the generation of RPE cells from pluripotent stem cells. It was shown that using RPE cells derived from hESC lines effectively improves photoreceptor survival in RPE-defective RCS rats [56]. These RPE cells also prevented the onset of secondary degenerative events [57].

Since the first case report of human homologous and autologous RPE transplantation for the treatment of exudative AMD in 1991 [58], more than 30 homologous

Table 1 Different cell sources and important growth factors/ chemical modulators used to promote retinal cell differentiation

Cell/ tissue type	Growth factor/chemical modulator	Primary differentiation	Reference
Fetal stem cells			
Retinal progenitors (r)	EGF, FGF2, heparine	Photoreceptors	[9, 10]
Neural retina progenitor cells (r)	FGF2 and NT3 (removal from medium)	Glial cells, neurons expressing rhodopsin, calbindin, calretinin	[82]
Progenitor cells neural retina (porcine)	CNTF and no EGF and bFGF	Photoreceptors	[11]
Human retinal progenitor cells	NT3, FGF2	Retinal cell (cell culture)	[12]
Retinal progenitor cells (m)	EGF	Mature neurons, rhodopsin, or cone opsin	[13]
Photoreceptor precursors (m)	Transplantation of cells into immature retina	Rod photoreceptors, synaptic connections	[14]
Retinal progenitor cells (h)	Transplantation of cells into 16 to 18 weeks G.A. B6 mice	Photoreceptors	[15]
ESC and iPSC			
ESCs (h)	Stepwise treatment with defined factors	Photoreceptors and RPE	[16]
ESCs and iPSCs (h)	Casein kinase I inhibitor, ALK4 inhibitor, the pho- kinase inhibitor	Retinal progenitors, retinal pigment epithelium cells and photoreceptors	[17]
iPSCs (h)	No bFGF	RPE (cell culture)	[83, 84, 85]
ESCs(h)	KOM, nicotinamide ,TGF	RPE (cell culture)	[86, 87]
ESCs (m)	bFGF, Dex, cholera toxin	A structure consisting of lens, neural retina, and pigmented retina(tissue culture)(cell culture)	[20]
ESCs(m)	NMDA-treated eyes	Eye-like structure	[21]
ESCs(h)	bFGF, xeno-free	RPE (tissue culture)	[88]
ESCs(m)	No LIF, retinoic acid	Neural progenitors , retinal cells	[23]
iPSCs(h)	KOS, zfbFGF, taurine, triiodo thyronin, hydrocortisone	RPE	[25]
Adult stem cells			
Dissociated cells from the RPE and the NR (m)	EGF, FGF2	Rod photoreceptors, bipolar neurons, and Müller glia	[32]
Adult iris, pars plana, and ciliary body progenitor cells	FGF2	Neurons and glia	[34]
Pars plicata and pars plana of the retinal ciliary margin progenitor cells(h)	FGF2, heparin, EGF	Photoreceptors	[35]
Multipotent cells within the IPE of postnatal and adult (r)	bFGF	Neural retinal cells, RPE, photoreceptors (cell culture)	[36]
Adult hippocampus-derived neural progenitor cells (r)	N2, bFGF	Retinal neurons	[41]
Hematopoietic progenitor cells (m)	SDF-1 α	RPE	[43]
Hippocampus-derived neural stem cells (r)	N2, bFGF	Neurons and glia	[46]
Adult CD90+MSC (r)	activin A, taurine, and EGF	Rhodopsin, opsin, recoverin	[48]
UCB-MSCs (h)	TGF β , CNTF, NT-3, BDNF	RGCs (superior colliculus)	[89]
Ciliary body (m)	bFGF, GDNF	Photoreceptor, bipolar cell	[90]
Iris(r)	FGF2	Rod photoreceptor	[91]

Key:

h — human

m — mouse

ESC — embryonic stem cells

iPSC — induced pluripotent stem cells

NR — neural retina

UCB — umbilical cord blood

MSC — mesenchymal stem cells

IPE — iris pigmented epithelium

RPE — retinal pigment epithelium

RGC — retinal ganglion cell

and 230 autologous RPE grafts have been performed [59]. The technique of harvesting RPE–choroid patch graft from the periphery, followed by insertion under the macula through retinotomy, was first described by van Meurs in 2003 [60]. It is now the most popular method of choice for RPE transplantation. Recent reports have shown that autologous RPE–choroid graft is able to produce sustainable long-term improvement in terms of vision and microperimetry performance, for neovascular age-related macular degeneration [61]. Other than autologous grafts, allogeneic and cultured HLA-typed cadaveric RPE cells have also been proposed for clinical application [62].

Photoreceptor

The mammalian retina contains highly specialized photoreceptors that are capable of capturing photons and transducing them into electrical signals. Replacing photoreceptors is much more challenging than RPE cells because the connection between photoreceptors and neurons are lost, and also because of the potential scarring response elicited. In 1999, Kwan [63] successfully transplanted photoreceptors in a mouse model of retinal degeneration. Outer segment reconstitution was observed in the recipient mice, and the mice were able to perform a simple light–dark discrimination test. Improvements in visual function have also been reported following transplantation of multipotent retinal progenitor cells derived from green fluorescent protein (GFP)-expressing mice [13].

Other transplantation strategies include grafting of retinal sheets, with or without attached RPE, into eyes of various rodent models of retinal degeneration [64]. Most recently, a few reports have demonstrated the ability of human neonatal photoreceptor precursors to differentiate and integrate into the outer nuclear layer (ONL) in both the intact and the degenerating retina of mature mice [14, 65]. Evidences has shown that photoreceptors and embryonic retinal tissue, when transplanted into the subretinal space, can form new synapses with existing host neurons. However, at the moment, photoreceptor transplants remain in the stage of laboratory science. The development of a combined tissue-engineered scaffold targeting both RPE and photoreceptors may be a promising direction for future research. Recent studies on stem cell therapy in retinal diseases are summarized in Table 2.

Methods of delivering stem cells

Currently the two most popular methods of delivering stem and progenitor cells into the eye are the intravitreal route and the subretinal route. The intravitreal route delivers stem cells into the eye through an injection using a small-gauge needle (e.g., 30-gauge). This method is technically easier and less

invasive. However, the cells have to migrate through the vitreous and inner retina to the outer retina. There are also no means of directing the cells toward the target treatment area. Some studies have demonstrated that, compared to subretinal injections, intravitreal injection of stem cells resulted in a higher survival rate and fewer invasions by immune cells [66, 67]. On the other hand, the subretinal delivery method is more technically demanding and more invasive. The cells are injected through the sclera and choroid, into the subretinal space, using a small-gauge needle. This method has the advantage of directing the cells towards targeted treatment areas. Some reports have shown that the subretinal route has resulted in better localization and differentiation of neural stem cells than the intravitreal route [68, 69]. Recently, there is a report of delivering stem cells subretinally on a biodegradable polymer composite graft [70]. Tomita and associates have shown a 10-fold increase in the number of surviving cells with this technique when compared to the conventional technique. In general, both routes have proved efficacious and are being routinely employed by stem cell researchers.

Potential obstacles and risks

Limitation of integration

Integration of graft cells into host tissue is another major obstacle at the moment. Wang et al. [55] reported their results following injection of both RPE cells of cell line ARPE-19 and human Schwann cells (hSC). By 15 weeks after injection, only hSC was able to form a monolayer of cells at the level of RPE. Despite displaying diploid properties and expressing RPE-specific markers, ARPE-19 cells did not show properties of RPE cells when injected and failed to form a monolayer of cells [71]. Klimanskaya [72] also observed that ESC-derived RPE cells remained aggregated when grafted, and failed to form a monolayer over the defective RPE in the subretinal space.

The reason for the behavior of grafted cells in failing subretinal expansion may be due to the high levels of retinoids within the host RPE cells. Retinoid is known to be able to inhibit cellular division, which may have also inhibited the transplanted cells from integrating. To overcome this limited integration, transplanting RPE cell sheets instead of RPE cells has been proposed [73]. Concomitant pharmacological modulations of the extracellular matrix may also improve host integration [74]. As transplantation techniques advance, future studies may incorporate more adjuncts to improve the integration of grafted cells into the host.

Inflammation and immunoreaction

Inflammation is activated in retinal degeneration primarily by microglia and macrophages [75, 76]. When a lesion is

Table 2 Recent studies on stem cell therapy in retinal diseases

Retinal diseases	Donor cell type (species)	Target (species)	Outcomes	Ref.
Retinal degeneration	h/mBM-SCs	Retinal cells (m)	Retinal degeneration rescued	[92]
	hBM- somatic cells	Photoreceptors (r)	These cells were differentiated into 3–6 layers of photoreceptors	[93]
	rBM- MSCs	Retinal cells (r)	Grafted cells expressed a rod photoreceptor and bipolar and amacrine cell markers	[94]
	Primate ESCs	Primate retinal cells	Co- culturing ESCs with ESC-derived RPE cells is efficient for inducing photoreceptors	[95]
	mESCs	Retinal cells (m)	ESCs differentiates to various retinal cell types	[96]
Neural retina repair	mPostmitotic rod photoreceptor precursor cells	Rod photoreceptors (m)	Photoreceptors were present up to 12 months post-transplantation	[97]
Retinitis pigmentosa	mBM-MSCs	Microglia (m)	These microglia plays a protective role in retinitis pigmentosa	[98]
Retinitis pigmentosa and AMD	hiPSCs	hRPE(culture)	iPSCs differentiate into functional RPEs which are comparable to fetal and ESC-RPE	[85]
AMD (clinical)	Autologous hRPE	Subfoveal space (h)	Autologous RPE transplantation restores vision in neovascular AMD	[99]
	Autologous hRPE	Macula (h)	Postoperative vision ranged from 20/200 to 20/64, with a 2-line increase in three patients.	[100]
Retinal dystrophy	hESCs	hRPE (r)	Improvement in visual performance was 100% over untreated controls	[101]
Glaucoma	hMSCs	Retinal ganglion cells (r)	BM-MSCs deliver neurotrophic factors and neuroprotection	[102]
Photoreceptor loss	hUTC, hPTC, hADF and hMSC	Photoreceptors (r)	Umbilical tissue-derived cells gave large areas of photoreceptor rescue; mesenchymal stem cells gave only localized rescue	[103]
	hRPE	Photoreceptors, rods and cones (r)	Partial preservation of rod and cone electroretinogram function	[104]
	hRPE/ hSCs	Photoreceptors (r)	hRPE and hSC grafts can survive and rescue photoreceptors	[105]
Macular degeneration	hESC- derived RPE	Photoreceptors (m/r)	The cells sustained visual function and photoreceptor integrity	[106]

Key:

AMD — Age-related macular degeneration

h — human (may added in before abbreviations)

m — mouse (may added in before abbreviations)

r — rat (may add in before abbreviations)

BM-SC — bone marrow stem cells

iPSC — induced pluripotent stem cells

ESC — embryonic stem cells

RPE — retinal pigment epithelium

UTC — umbilical cord tissue-derived cells

PTC — placenta tissue-derived cells

ADF — adult dermal fibroblasts

MSC — mesenchymal stem cells

SC — stem cells

identified, these cells form a barrier around the lesion, separating damaged tissue from the undamaged [77]. Activated microglia and macrophages produce inflammatory cytokines including IL-1b, IL-6, tumour necrosis factor-alpha (TNF-a), nitric oxide and reactive oxygen species [75]. Inflammatory cytokines have been implicated in signalling migratory pathways for progenitor cells, in the hope of replacing the defective or dead cells [78]. However,

excessive cytokines maybe toxic to grafted cells. They have to overcome the pro-inflammatory reaction as well as gliotic barriers, which may hinder its proliferation. Furthermore, microglial cells can serve as antigen-presenting cells, and the immune reaction produced may destroy allografts or xenografts. This poses a major obstacle to the long-term survival of allogeneic RPE or photoreceptor grafts. The eye and brain have been considered to be immune-privileged sites, partly

because of the existence of the blood–retinal, blood–brain barrier. However, these barriers are often compromised in injured or diseased retina, and blood vessels may become ‘leaky’ [79]. At present, many transplanted photoreceptor progenitors die following allografts [14]. Graft rejection without immunosuppression may lead to graft rejection [80]. Therefore, immunosuppression may be required at least until the blood–retinal barrier has regained its function after surgery.

Tumorigenicity

At the moment, no evidences of tumorigenesis have been reported when human ESC-derived retinal progenitor cells were used [23, 56, 68, 81, 82]. However, there has been one report of tumor formation when neurally selected mouse ESC was transplanted into rodent retina [83]. Therefore, it is vital that a stringent selection process to eliminate any undifferentiated ESC before applying into human trials.

Another potential risk for tumorigenicity is if the cell cultivation period has been prolonged. Djojsubroto [39] reported that chromosomal aberration accumulated rapidly upon prolonged cultivation in ciliary body-derived cells. This maybe potentially tumorigenic; hence, great care must be taken not to prolong the cultivation period.

Future developments

The use of stem cells in treating retinal degenerative disease has clearly demonstrated great potential for restoring vision. Several issues, however, remain unsolved. A well-defined technique together with a more sustainable and acceptable source of donor cell line have to be sought. At present, stem and progenitor cells transplantation are popular, but in the future, cell-sheet transplantation may be more applicable as it has the advantage of overcoming the problem of integration. However, surgical challenges and the shortage of donor cells are yet to be solved. The continuing search for a sustainable cell source is ongoing. ESC, iPSC, marrow-derived stem cells, umbilical cord-derived cells, and immortalized cell lines are potential candidates. To improve therapeutic effects, an alternative strategy is to combine cell transplantation with gene therapy. A combination of RPE and photoreceptor with anti-angiogenic factors (e.g., anti-vascular endothelial growth factor) may potentially increase cell viability and engraftment.

Conclusions

In this review, we have presented the current state as well as possible future directions of stem cells therapy for degenerative

retinal diseases. While the great potential of stem cell therapy for restoration of visual functions has been clearly demonstrated, several issues are yet unresolved. Appropriate cell sources, targeted cell types for therapy, delivery techniques, and potential risks have to be carefully evaluated before translating into clinical trials. With the development of stem cell biology and technical breakthroughs, clinical translation of RPE transplantation to reconstitute the subretinal anatomy and improve photoreceptor function will hopefully bring hope to the blind.

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