<table>
<thead>
<tr>
<th>Title</th>
<th>Promises of stem cell therapy for retinal degenerative diseases</th>
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<tr>
<td>Author(s)</td>
<td>Wong, IYH; Poon, MW; Pang, RTW; Lian, Q; Wong, D</td>
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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

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 multi-
potent 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 retinal-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 Djojosubroto [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 investiga-
tions 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 neurochem-
ical 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 intra-
vitreal 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 multi-
lineage 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

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

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
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-1β, IL-6, tumour necrosis factor-alpha (TNF-α), 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

Table 2 Recent studies on stem cell therapy in retinal diseases

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

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
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. Djojosubroto [39] reported that chromosomal aberration accumulated rapidly upon prolonged cultivation in ciliary body-derived cells. This maybe potentially tumorigenetic; 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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