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MINIREVIEWS

New frontiers in retinal transplantation

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Abstract

New frontiers about retinal cell transplantation for retinal degenerative diseases start from the idea that acting on stem cells can help regenerate retinal layers and establish new synapses among retinal cells. Deficiency or alterations of synaptic input and neurotrophic factors result in trans-neuronal degeneration of the inner retinal cells. Thus, the disruption of photoreceptors takes place. However, even in advanced forms of retinal degeneration, a good percentage of the ganglion cells and the inner nuclear layer neurons remain intact. This phenomenon provides evidence for obtaining retinal circuitry through the transplantation of photoreceptors into the subretinal region. The eye is regarded as an optimal organ for cell transplantation because of its immunological privilege and the relatively small number of cells collaborating to carry out visual activities. The eyeball's immunological privilege, characterized by the suppression of delayed-type hypersensitivity responses in ocular tissues, is responsible for the low rate of graft rejection

in transplant patients. The main discoveries highlight the capacity of embryonic stem cells (ESCs) and induced pluripotent stem cells to regenerate damaged retinal regions. Recent progress has shown significant enhancements in transplant procedures and results. The research also explores the ethical ramifications linked to the utilization of stem cells, emphasizing the ongoing issue surrounding ESCs. The analysis centers on recent breakthroughs, including the fabrication of three-dimensional retinal organoids and the innovation of scaffolding for cell transportation. Moreover, researchers are currently assessing the possibility of CRISPR and other advanced gene editing technologies to enhance the outcomes of retinal transplantation. The widespread use of universally recognized safe surgical and imaging methods enables retinal transplantation and monitoring of transplanted cell growth toward the correct location. Currently, most therapy approaches are in the first phases of development and necessitate further research, including both pre-clinical and clinical trials, to attain favorable visual results for individuals suffering from retinal degenerative illnesses.

Key Words: Retinal transplantation; Retinal stem cell; Human embryonic stem cells; Pluripotent stem cells; Retinal tissue transplant

Core Tip: Current technology using stem cells and grafted tissues is of great interest when dealing with retinopathies. Research has increased in recent decades, but most are still *in vitro*. Using and manipulating stem cells is not simple and involves many ethical concerns. However, there have been some good outcomes regarding the effectiveness of grafted cells in integrating into degenerated host retinas to restore vision in some form.

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INTRODUCTION

To cure retinal degenerative illnesses, including age-related macular degeneration (AMD) and retinitis pigmentosa (RP), new developments in retinal transplantation by photoreceptor cell replacement are viewed as an appealing avenue to restore visual function. Modern technology makes it possible to create retinal organoids that are self-organizing from induced pluripotent stem cells (iPSCs) or human (or mouse) embryonic stem cells (hESCs). In cases with late-stage retinal degeneration, the possibility of transplanting retinal tissue offers a stable layer of retinal cells that are qualitatively equivalent to prenatal retinal cells without posing moral or legal dilemmas[1-3]. Transplantation of hESC/iPSC-retinal tissue sheets or cells has been led in animal models with late-stage retinal degeneration, and it has displayed functional potential to permit light responses in host retinal ganglion cells (GCs). PSC-derived retinal sheets transplanted *in vivo* have successfully formed well-structured photoreceptor layers capable of transmitting light signals to retinal cells and maintaining neural contact with the host bipolar cells[4-6].

To date, no surgical or pharmacological solution effectively regenerates the degenerative retina or avoids the progress of vision loss. However, research has focused on stem cells and innovative cell technologies for some years. Recent studies have shown that retinal transplantation of cells or tissues has excellent potential, but information about new retinal microenvironments after transplantation is still limited. For this reason, huge investments, resources, and some clinical trials have been performed in different laboratories worldwide.

In preparing the manuscript, we used (https://www.referencecitationanalysis.com) Reference Citation Analysis and (https://pubmed.ncbi.nlm.nih.gov) PubMed. The search words considered included "retinal transplantation" (4955 papers) and "retinal stem cells" (6312 publications) for manuscripts published between the 1st of January 2000 and the 31st of January 2024. We only considered papers published in English with a structured text and abstract. We excluded "case reports", "case series", "conference papers", and "letters". In this review, we will focus on analyzing current investigations involving stem cells as a new viable treatment for human retinal diseases.

STRUCTURE OF THE RETINA

Integrating visual signals occurs when the neurosensory retina is active. Photoreceptors absorb light, sending signals through interneurons to bipolar cells and retinal GCs, with axons making up the optic nerve. Amacrine cells regulate the data flow between retinal GCs, bipolar cells, and horizontal cells. These cells adjust the information flow from photoreceptors to bipolar cells and fine-tune visual signals throughout the pathway[7].

A lengthy stalk connects the photoreceptor cell body to the inner segments, which house most of the cell's catabolic and biosynthetic machinery. The apparatus for absorbing a unit energy of light radiation and transforming it into electrical energy. This occurs in the outer segments, albeit the biomolecular mechanism remains unknown (Figure 1). The photoreceptor layer is the outermost segment and comprises a regenerative stack of disc membranes piled into the outer segment's base[8]. The retinal pigment epithelium (RPE) phagocytizes the disc membranes at the tip, which are shed daily. Retinal degeneration follows disc membrane pooling in the subretinal region due to damage and decreased phagocytosis (Figure 1).

The outer blood-retinal barrier comprises the fenestrated choriocapillaris, RPE, and Bruch's membrane. The RPE is characterized by its polarity and ability to distribute several ion pumps, membrane receptors, and transporters in a specific manner to either the basolateral or apical membrane[9,10].

As a result, RPE can move waste materials and nutrients in different directions from the choriocapillaris to the neurosensory retina. For photoreceptor function to occur, the RPE must be able to maintain the subretinal space's ionic microenvironment[11]. At the basolateral membrane, receptor-mediated endocytosis absorbs vitamin A and transforms it into 11-cis-retinal, the cofactor for photoreceptors' light-sensitive opsins. All trans-retinal factors, including 11-cis, are transferred back and forth during the visual cycle between RPE and photoreceptors, which is mediated by interactions throughout the subretinal region. RPE cells phagocytize the outer segments of photoreceptors, preserving Bruch's membrane and the choriocapillaris[12]. Much research is about Bruch's membrane structure and functions, where drusen accumulates[13]. Drusens are yellow aggregates of proteins and lipids that can damage the permeability barrier of Bruch's membrane. Retinal degeneration following photoreceptor degeneration depends on the degradation of the choriocapillaris or the underlying RPE[14].

RP

RP refers to a collection of genetic disorders that cause the progressive degeneration of tapeto-retinal cells. This category of inherited illnesses is characterized by about 3000 mutations in around 80 genes, resulting in the gradual degradation of the rod and cone photoreceptors. Ultimately, this leads to complete loss of vision or loss of vision in specific areas[15]. The processes of phototransduction, rhodopsin cycling, and cell trafficking are gradually disrupted or significantly changed, resulting in the characteristic clinical features of bone spicule retinal deposits, pallor in the optic nerve head, and abnormalities in the retinal vasculature[15].

Patients in the early phases of RP suffer from nyctalopia and peripheral visual field loss. Still, in the late stages, the severe loss of cones brings about a loss of color discrimination and visual acuity. RP can be categorized into many inheritance patterns, including autosomal recessive (50%-60% of cases), autosomal-dominant, mitochondrial (30%-40% of cases), and X-linked RP (5%-15% of cases). Patients with X-linked inheritance patterns generally exhibit a more unfavorable prognosis compared to individuals with other inheritance patterns[16]. Hartong e*t al*[17] assessed the impact of RP on the daily lives of patients and reported that the disease critically impaired the ability to work[17]. Reduced quality of life and dependence on carers were other burdens reported in their study while the carers also reported psychological and physical stress.

Possible interventions aim to postpone the progression of retinal degeneration, although no definitive efficacy has been established. Dietary supplements (docosahexaenoic acid, vitamin A, lutein, *etc.*) have not shown a real benefit aside from a small subset of individuals with high baseline cone amplitudes[18]. Neuroprotective agents and compounds, such as valproic acid, human ciliary neurotrophic factor, and topical unoprostone isopropyl, have demonstrated limited but encouraging efficacy in treating retinal degeneration[19]. Topical or oral carbonic anhydrase inhibitors, anti-vascular endothelial growth factor agents, and steroids can be considered for treating cystoid macular edema, present in about 20% of the cases. Still, visual acuity has not significantly improved[20]. Subretinal, epiretinal, and suprachoroidal retinal prosthetic devices have been considered to provide visual perception to patients affected by severe forms of RP. Several regulatory organizations have approved a limited number of prosthetic implants, such as the one developed by Alpha IMS, a German business, and the Argus II implant from Second Sight Medical Products, based in the United States. Although these devices are costly and require long surgical training to be implanted, their visual improvement has undoubtedly improved the quality of life in the subset of patients eligible to receive these devices[21-22].

In 1990, the discovery of rhodopsin mutation as a cause of autosomal-dominant RP paved the way for gene therapy development, which could be used to manipulate the mutated gene expression with different treatment techniques[23]. Gene delivery treatments include Adeno-Associated Virus-based RPE-65 (*i.e.*, Luxturna™, Spark Therapeutics, PA, United States). These vector-based treatments correct the biallelic *RPE65* gene mutations that cause several variants of RP and Leber's congenital amaurosis. Numerous experiments are being conducted to provide the proper copy of the mutant genes or inactivate mutant genes *via* gene editing using the CRISPR/Cas system[24]. Base and prime editing gene tools provide considerably more accuracy in making genomic alterations. Base editing enables the direct conversion of a specific DNA base pair into another, while prime editing combines the functionalities of CRISPR and reverse transcriptase to achieve precise insertions and deletions. These approaches have demonstrated promise in preclinical models for rectifying mutations linked to retinal dystrophies. The main problem is that the vast heterogeneity of the causative genes is an obstacle to developing a universal gene therapy valid for all types of RP. Research on therapies that can be universally applied to this hereditary disease is also underway, for example, by reactivating the dormant cones by restoring glucose transport or rebuilding the retinal circuitry using optogenetics[25].

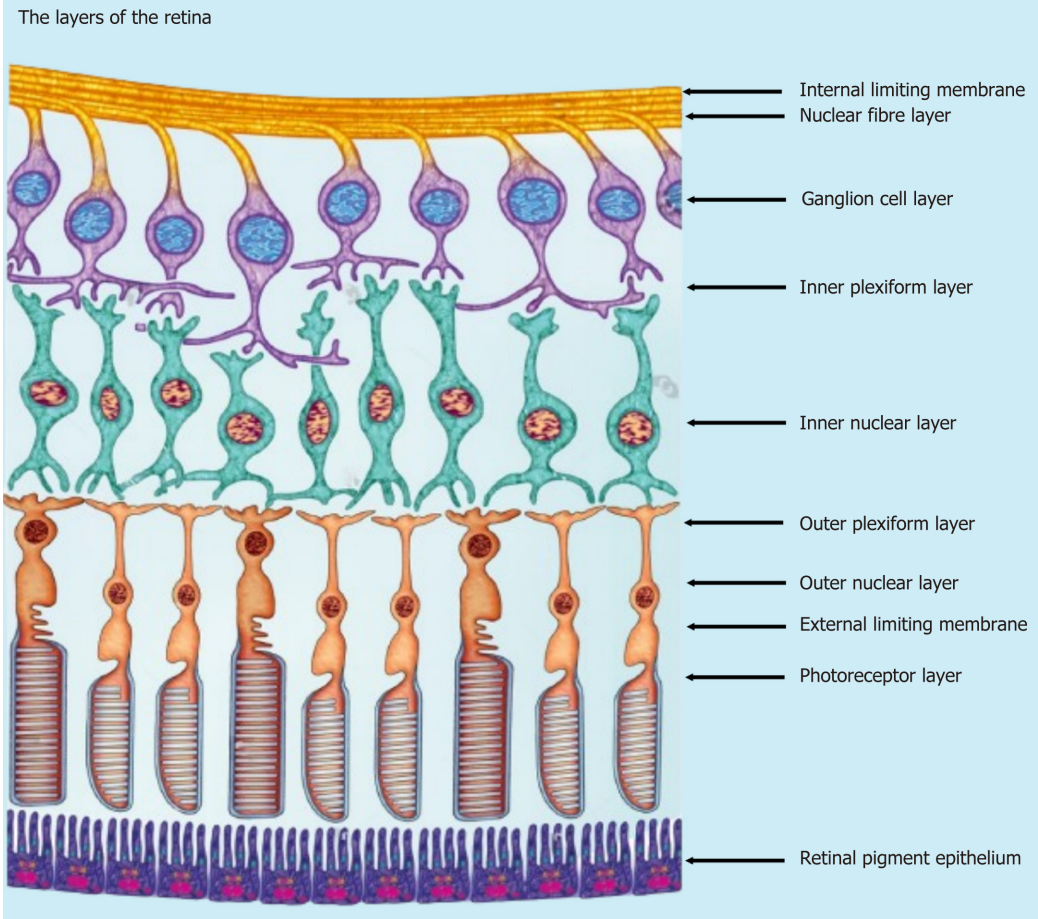

Figure 1 Retinal structure.

AMD

AMD affects millions of people worldwide. It is estimated that more than 22 million people in the United States will have AMD by 2050. This disease remains the most prevalent cause of visual impairment in geriatrics in developed countries, posing and elevated all-cause mortality ratio of 1.46[26]. In the early stage, dry AMD involves the RPE and then progresses with photoreceptor disruption. Wet AMD affects the RPE, choriocapillaris, and deep capillary plexus with aberrant neovascularization[27]. Geographic atrophy represents the final stages of macular degeneration, involving the complete loss of photoreceptors, RPE, and macular choriocapillaris. To date, no effective treatment exists for late-stage AMD.

AMD is a multifactorial disease, meaning that many genes and proteins are involved. Therefore, AMD is not treatable by correcting just a single or a few mutations. For preclinical research and clinical trials, scaffolds have been used to reconstruct RPE layers with the nearby choroid. Scaffolds permit the organization of the orientation of photoreceptor cells and ensure the overlap between RPE and photoreceptors[28]. Theoretical scaffolds provide an optimal environment to promote the adherence, viability, and controlled specialization of RPE and/or retinal progenitor cells. Of course, scaffolds must be nontoxic and surgically implantable. They also need to be very thin, less than 10 μm, to guarantee the following aspects: Transient mechanical stability after implantation, no change of the focal length of the eye, and flexibility to the retinal curvature. Biodegradable scaffolds should be the best option because of the following features: Lack of subretinal foreign material, little effect on the focal length of the eyeball, enhanced vascularization, and better merge between the new RPE sheet and the host RPE. Several studies have examined the natural and synthetic scaffolds for retinal culture[29, 30]. Scaffolds with stem cells are now in research trials and have shown to be somewhat effective and safe, even if the trials are still too small to be significant.

The subretinal space, a key target for implanted scaffolds, separates the complex neurosensory retina from the pigment epithelium monolayer. This space, which contains fluid accumulated by the RPE, serves as a region of interconnection for RPE microvilli. It is also the site of neurosensory detachment. The macula, located temporal to the optic disc, is a highly pigmented area with an abundance of cone photoreceptors. These cones, responsible for color detection and high visual detail resolution, contribute to fine vision. On the other hand, the extramacular area, useful in low light situations, contrast sensitivity, and motion detection, plays a different role. A subretinal scaffold can be created by injecting selected fluids (specifically RPE neo-tissue) into this space to create a pseudo-detachment and then the resulting space can be used for an RPE transplant. Subsequently, the retina achieves homeostasis and there is reattachment of the retinal detachment created by the initial injection into the subretinal space[31,32].

The transfer of photoreceptors can be done in two ways: As a liquid matrix or as a pre-prepared retinal sheet. A skilled surgeon administers the preparation in the subretinal space. These pre-prepared photoreceptor cells have the ability to rejuvenate connections with the receivers' existing bipolar cells. The advantage of the retinal sheet is that it provides extended viability for the graft, is less prone to immunogenicity, and can be easily monitored using electron microscopy [33]. As the graft heals, a multi-layered structure forms, resembling maturation[33]. However, there is a possibility that ESC/iPSC-retinal-based sheets may affect the host-graft integration. The Muller cells glia, a different form of host cells, are equally crucial for generating the outer segment architecture, enhancing glutamate absorption, and recycling the photosensitive pigments (especially for the cone photoreceptors). Horizontal cells form ribbon synapses and play a role in integrating and regulating chemical signals from photoreceptors. The removal of horizontal cells leads to the degeneration of photoreceptors. Studies have shown that bipolar cells in retinal sheets act as a barrier, preventing the host bipolar cells from making contact and establishing connections with graft photoreceptors[34].

FEATURES FOR GOOD OUTCOMES IN RETINAL TRANSPLANTATION

Animal models of RP demonstrate the probability of sparse synapses between transplanted cells and interneurons to host bipolar cells. The low success of this kind of cellular integration is that grafted cells often fail to establish functional synaptic circuitry. Biologically, the RP retina is featured by extensive remodeling with dramatic rod neurite sprouting, incredibly close to the areas of photoreceptor death. Neurite sprouting is also seen in amacrine and horizontal cells, and rods extend neurites along activated Muller cells, leading to changes in retinal homeostasis[35]. Changes in the retinal microenvironment can impact the activity of the transplanted cells, leading to inconsistent growth of nerve fibers and failure to form connections with target cells.

Current research utilizing animal models of outer retinal degeneration has identified issues associated with the lack of synapse development with the host retina. The survival and integration potential of transplanted photoreceptor cells relies on the embryonic stage of the transplanted cells. The transcription factor Nrl, exclusive to rods that no longer divide, is of interest. A study involving the transplantation of photoreceptor cells that produce green fluorescent protein and are regulated by Nrl into a mouse model with stationary night blindness caused by Gnat1 deficiency has shown that the transplantation of immature postmitotic photoreceptor precursor cells had the highest likelihood of successful integration[36]. Moreover, the stage of outer retinal degeneration substantially affects the integration of transplanted cells into the recipient retina. When photoreceptor cells are integrated into the host retina, their success may depend on physiological factors such as the extent of damage to glial tissue and the state of the outer limiting membrane (OLM) as the disease advances[37].

Analyzing the findings from the investigations can offer additional elucidation. The ability of photoreceptor grafts to connect well in Gnat1−/−; Rho−/− mice reduces when the OLM experiences more severe and prolonged retinal degeneration. In contrast, the Prph 2 +/Δ307 animals exhibited a direct relationship between the progression of outer retinal degeneration and the augmentation of host integration. Moreover, it was disclosed that the maintenance of OLM integrity was insufficient in these models. This is remarkably accurate when confronted with declining glial tissue. Integrating the newly introduced photoreceptor matrix remains unchanged as the disease advances in the PDE6βrd1/rd1 mutant, where the OLM is severely disrupted. However, gliosis continues to advance with disease development. In addition, the milieu in which outer retinal cells deteriorate hinders their capacity to move and establish connections.

Glial cells significantly increase the production of chondroitin sulfate proteoglycans while forming gliotic scars. This mechanism additionally restricts the movement of cells, the ability of axons to change and adapt, and the process of regeneration. Factors such as reducing the weakening of gliosis in the retina, intentionally disrupting the OLM, or breaking down the chondroitin sulfate proteoglycans using enzymes have been found to enhance the integration of transplanted photoreceptor cells onto the recipient's retina[38,39].

Animal experiments confirm that postmitotic rod precursor cells will most likely successfully synapse with the host retina[40]. Due to strict laws and ethical issues, human fetal tissue is unavailable, so scientific interest is in the potential to generate new photoreceptor precursors from stem cells. Pluripotent ESCs remain a potential source of generating photoreceptor cells[41]. The pluripotency of these stem cells has been proven through their differentiation into several retinal cell types, such as rod and cone photoreceptors, when transplanted into the subretinal space of rodent and primate retinal degeneration models. Studies on transplantation of photoreceptor precursors produced from ESCs have demonstrated that these precursors establish stronger connections with the surrounding tissues of the host when transplanted during the earlier stages of development. Nevertheless, the allogeneicity of ESC-derived grafts raises concerns about immune-mediated rejection. The nuclei of stratified somatic cells can be reprogrammed to pluripotency by inducing the expression of four transcription proteins: Oct4, Sox2, c-Myc, and Klf4. The advantage of these are that they are not affected by the hosts' immune system and can be stimulated to differentiate into needed retinal specific cells [41]. An added bonus is that 3D retinal organoids can be synthesized from such stem cells and used to mass produce photoreceptor cells for both transplantation and research[42-44].

MICROENVIRONMENT FOR THE RETINAL TRANSPLANTED CELLS

Regardless of their type and synapses with host tissue, cells transplanted into the subretinal space may increase the survival potential of preserved retinal neurons. This ability to communicate with host cells has been described in work by Tezel and Ruff[44], who showed in an outer retinal degeneration model of *Rho*$^{P[23]\ H/+}$ mice[43,44]. The fact that cone

photoreceptors outlast rod cells during RP might depend upon greater glucose delivery from RPE cells, which may help maintain high metabolic functions and regenerate their outer segments.

Another interesting stem cell type is the umbilical stem cell. These may be a combined preparation of mesenchymal stem and hematopoietic cells obtained from umbilical cord tissue or blood. In animal retinal degeneration models, the trophic effect of transplanted umbilical cells was linked to the rejuvenation of RPE phagocytosis in a study involving Royal College of Surgeons rats. It was theorized that by secreting several humoral factors and bridge molecules, umbilical stem cells enhance photoreceptor outer segment bonds with the RPE[45].

Stem cells from the bone marrow can differentiate into several animal cell types, including neural cells. Reports indicate that these cells may express some retinal markers, which have beneficial effects through paracrine mechanisms. Studies show that mesenchymal stem cell secretomes possess neuroprotective properties; thus, they may mitigate photoreceptor loss *via* paracrine signaling[46,47].

A summary of the scaffolding techniques and outcomes sampled in this study is shown below (Table 1).

SAFETY ISSUES

To produce human embryonic or pluripotent stem cells, it is necessary to implement rigorous quality control measures. These measures ensure that the cells remain stable and consistent in their creation, while also eliminating any potential risks of tumor formation, toxicity, or immune reactions. Hence, the Food and Drug Administration must take into account the necessary technology for initiating and sustaining human stem cell lines before they are used in regenerative therapies while formulating regulations for stem cell production. Excessive utilization of stem cells can result in serious issues that can impair vision. Therefore, it is crucial for regulatory agencies to provide sufficient and appropriate measures to ensure safety[48-52].

Spontaneous proliferation and differentiation potentials of both human ESCs and induced pluripotential stem cells account for the risk of teratomas. A study reported a 50% incidence of teratomas after eight weeks in an animal model after receiving ESC into the subretinal space[53]. Hence, screening tests are essential to detect malignant transformation and complex morphogenesis/organogenesis.

Another major safety issue that arises during the creation of iPSCs is the incorporation and utilization of viral gene fragments and genetic transcription factors. These bear the potential to trigger drastic endogenous genetic and epigenetic alterations. Potentially, transplant therapy may result in tumor formation post-transplantation[54]. Other paracrine techniques have been developed to avoid this risk of teratogenic mutation, including the use of the Sendai virus[55]. It highlights the significance of adequately monitoring the genetic and epigenetic material during the human proliferation process, as reprogramming somatic cells has the ability to modify genome integrity of the parent cell or hide any chromosomal abnormalities. Several investigations have shown the presence of chromosomal aberrations and mutations in the mitochondrial genome following cell reprogramming procedures[56,57]. Occasionally, increased apoptosis, rapid telomere shortening, severely limited growth and expansion capability, and early senescence occur.

Although immune response should not be evoked by iPSCs, immunogenic reactions represent an issue with using human ESCs. The following strategies have been shown to prevent human ESCs-derived immune-mediated rejection: cell sheathing, introduction of a somatic cell nuclear transfer to repurpose the same individual's somatic cells into needed stem cells, genetic engineering to mitigate the surface expression of human leukocyte antigen (HLA), and hematopoietic stem cell or bone marrow transplantation to induce hematopoietic chimerism[58].

To date, computer-based algorithms are used to match-make compatible immunogenic donor HLA types to suitable hosts to attenuate or eliminate immune responses and improve the chances of transplant survival. Published data on the transplantation of solid organs have shown that combinations of HLA-B, HLA-A, and HLA-DR factors are essential to long-term graft survival, immunosuppressive regimen notwithstanding[59]. Although this modality may be deemed adequate, extensive resources are needed to develop large HLA-matched ESC banks, with consequent medico-legal concerns associated with undertaking such ventures. Establishing a Haplobank of human ESCs is an immense technical challenge because the HLA system is complex and consists of nearly 10000 HLA-I and II alleles[60].

Innovative therapeutic approaches for retinal degenerative disease utilize mixed gene engineering and regenerative medicine applications. For instance, essential cell fate regulator genes can be deleted or engineered to yield ideal cell types within retinal grafts: These are often comprised of vital cells that attain pre-determined forms at maturity post-transplant. The exclusion of the *ISL1*$^{-/-}$ in hESC retinas caused a reduction of ON-bipolar cells, which are the second neurons receiving photoreceptor signal, sparing the photoreceptor cells, Müller cells, and horizontal cells; gene editing, in this case, allowed functional host-graft integration after transplantation. Matsuyama *et al*[61] investigated detailed phenotypes of *ISL1* gene deletion in hESC-retina by observing adult graft photoreceptors that showed phototransduction cascade proteins after transplantation in an organized manner[61]. A comparative study revealed that *ISL1*$^{-/-}$ hESC-retinas had better host-graft contact, resulting in higher light sensation in the host RGCs than wild-type hESC-retinas. Yamasaki *et al*[62] suggested multiple synaptic markers demonstrated the host-graft synapse formation[61,62].

Research data also shows that adding 9-cis retinol to transplanted retinas induced an ability to respond to repeated light stimuli. This was achieved after isolating the transplanted retina from the RPE without rod/cone opsin recovery. This discovery suggested that microenvironmental conditions play a crucial role. In addition, it was reported that HLA class I or glial fibrillary acidic protein enhancement was restricted to the RPE portion of the graft rosettes, which did not attach to the host retina. This shows that nonintegrated photoreceptors can be susceptible to post-transplantation degeneration[62].

Table 1 Scaffolding with stem cell-derived cells

Scaffold	Characteristics	Disease	ETDRS improvement (letters)
	hESC-RPE: 50-150000 cells	Dry AMD	12
PET	hESC-RPE (approximately 100000) on 10 μm-thick PET, coated with plasma-derived vitronectin; Non-biodegradable	Wet AMD	21
Parylene	hESC-RPE (approximately 100000) on ultrathin (0.3 μm-thick), parylene membrane on a perforated, 6 μm-thick parylene support; Biodegradable	Dry AMD	17
PLGA	hiPSC-RPE (approximately 100000) on 10 μm-thick, electrospun PLGA with 350 nm mean fiber diameter; Biodegradable	Dry AMD	In progress
hiPSC- secreted basal membrane	hiPSC-RPE on PET coated with a collagen-I gel; Confluent sheets released from PET with collagenase Biodegradable	Wet AMD	No change

AMD: Age-related macular degeneration; hESC-RPE: Retinal pigment epithelium derived from human embryonic stems cells; hiPSC-RPE: Retinal pigment epithelium derived from human induced pluripotent cells; PET: Polyethylene terephthalate; PLGA: Lactic-co-glycolic acid.

Further analysis of immunohistochemistry findings suggests the presence of essential factors for graft-driven retinal reconstruction, likely derived from the local microenvironment. Rejuvenating the ability to sense light positively correlates with the contact quality at the host-graft junction. This may be achieved by lowering graft inner cells in ISL1−/−hESC-retinas, featuring more viable host inner plexiform layer architecture. On the other hand, the thicker layers observed on the RPE area consisting of graft inner cells (as seen in wild-type hESC-retinas) may attenuate visual pigment recycling *via* RPE in the graft. Graft photoreceptor layer (ONL) thinning due to graft transplantation at the latter phases of differentiation potentially expresses a decrease in graft inner cells. This may, in turn, play a supportive role in the inner cells for photoreceptor viability and growth. Therefore, it can be assumed that there might be an inevitable trade-off between ONL thickness and direct contact with the host-graft. The negative correlation between the inner segment/outer segment status and retinal GC responsiveness can indicate this trade-off. It is instructive that abundant viable photoreceptors concerning host-graft integration, contact, and inner plexiform layer preservation are most important to the success of the graft, especially as reported in *ISL1*$^{-/-}$hESC-retinas[63].

Some interesting studies have attempted to replace the outer retina using a sheet created ex-vivo comprising photoreceptors differentiated from stem cells. To be effective, the newly grafted photoreceptors need to connect with neurons in the host retina, allowing environmental light to pass through these retinal cells and then to the brain.

Other authors, specifically an Asian research team led by Michiko Mandai, stated that connecting the grafted sheet to bipolar cells in the host retina proves very difficult. Naturally, retinal sheets contain their bipolar cells. The final issue in having an effective retinal sheet is to ensure any bipolar cells are discarded at the end stages of photoreceptor maturation. Therefore, investigators targeted *ISLET1*, a gene that encodes for bipolar cell maturation and stimulates its attachment to photoreceptors. These researchers created mutated human stem cells that were missing the *ISLET1* gene. They then used these mutated human stem cells to develop retina organoid sheets. There was no disparity or difference between the resulting retinal sheets from these clone stem cells and those created using normal human stem cells, and they were all deemed functional and deemed to have proper organization[64].

By transplanting new retinal sheets into degenerated rat retinas that had demonstrated near-complete loss of photoreceptors, many tests showed that photoreceptors in the transplanted retinal sheet were appropriately attached to the host retina. The data also revealed that these retina sheets matured properly after grafting to the host eye. To test an effective better response to light, the authors measured the function of the retinal GCs. They reported an excellent response to light, indicating that more photoreceptors in the graft sheet were connected, with a better response in these cloned sheets than sheets from normal human stem cells[65,66].

ETHICAL CONSIDERATIONS

Undoubtedly, it is crucial to discuss the ethical implications associated with utilizing stem cells, particularly ESCs, in retinal transplantation to provide a well-rounded viewpoint. ESCs are obtained from the inner cell mass of a blastocyst, which is an embryo in the early pre-implantation stage. The utilization of these cells in scientific investigation and medical treatment is a subject of controversy owing to various ethical considerations: The acquisition of ESCs necessitates the destruction of the embryo, giving rise to notable ethical considerations. Critics contend that this method is ethically objectionable due to its involvement in the termination of potential human life[67]. This viewpoint is frequently based on diverse theological and philosophical convictions that consider the embryo to possess moral significance starting from the instant of conception[68]. There are reservations over the process of obtaining informed consent for the donation of embryos for scientific purposes. It is of utmost importance to guarantee that contributors possess a comprehensive understanding of the consequences and are not subjected to coercion or undue influence. Advocates of ESC research contend that the utilization of these cells is warranted due to the prospective advantages, such as the development of therapies for incapacitating disorders such retinal degenerative diseases. In addition, a significant number of embryos

utilized in research are excess embryos resulting from in vitro fertilization treatments, which would otherwise be disposed of.

Regarding iPSCs, these are created by genetically reprogramming adult cells to resemble ESCs[69]. This method of obtaining stem cells raises fewer ethical problems compared to other approaches. These iPSCs circumvent the need for embryo utilization or destruction, rendering them morally preferable to a significant number of individuals. These cells can be obtained from the individual's own cells, reducing the chances of immunological rejection and eliminating ethical concerns associated with donor permission. Nevertheless, ethical questions persist with iPSCs, particularly over the enduring safety of employing genetically edited cells and the possibility of unanticipated repercussions[70].

Irrespective of the specific type of stem cells employed, there exist ethical concerns pertaining to fairness and availability. Stem cell therapies might incur significant costs, potentially leading to a scenario where only individuals with financial means can get these treatments, thereby worsening pre-existing disparities in healthcare access. There is surely issues about global disparities. Variations in regulatory frameworks and the accessibility of resources among nations may result in inequalities in the distribution of benefits from developments in stem cell therapy. It is essential to provide comprehensive information to patients and donors regarding the potential hazards, advantages, and uncertainties linked to stem cell therapy. If volunteers are used, it is crucial to guarantee that permission is willingly provided, without any kind of coercion or undue influence, especially when dealing with vulnerable populations. Robust regulatory frameworks are necessary to safeguard the safety, effectiveness, and ethical standards of both research and clinical application of stem cells. Stem cell therapies must undergo thorough testing and approval procedures to guarantee their safety and effectiveness prior to their widespread use in clinical practice. It is imperative to conduct post-market surveillance and long-term follow-up studies in order to evaluate the impacts of stem cell therapies and address any emergent ethical or safety concerns.

CONCLUSION

In recent years, the science of retinal transplantation has experienced notable progress, especially in the areas of stem cell research and gene editing technology. Studies have shown interesting results through the transplanting of RPE cells produced from both hESCs and iPSCs. These cells have been shown in clinical trials to be able to merge with the host retina, improve visual function, and slow down the course of diseases such as AMD. Progress in 3D retinal organoid technology has facilitated the development of more intricate and operational retinal tissue in a laboratory setting. These organoids have the ability to replicate the structure and function of the human retina, making them a more efficient tool for investigating retinal illnesses and evaluating prospective treatments.

The utilization of CRISPR-Cas9 gene editing has made substantial progress in the treatment of inherited retinal disorders. Recent trials have investigated the use of CRISPR to rectify genetic abnormalities associated with RP and Leber congenital amaurosis. These trials have shown encouraging first outcomes in enhancing retinal function.

The progress in creating biocompatible scaffolds that facilitate the survival and integration of transplanted retinal cells has been significant. For instance, research has demonstrated that using biodegradable materials and hydrogel-based scaffolds can improve the structural and functional integration of retinal grafts. Nanoparticles and other nanomaterials are employed to enhance the targeted delivery of medicinal medicines to the retina, hence improving effectiveness and minimizing adverse effects. These technologies facilitate the regulated release and precise distribution, which are essential for the effectiveness of retinal transplantation and gene therapy.

Several promising technology and innovative approaches are expected to greatly impact the future of retinal transplantation research, which include: The incorporation of artificial intelligence (AI) in the diagnosis and treatment planning; AI in stem cell differentiation; CRISPR-Cas13 cutting-edge gene editing techniques; epigenome editing; improved cell delivery and integration; utilization of 3D bioprinting to create intricate retinal structures; optogenetics that involves using light to control and manipulate the activity of cells in living organisms; regenerative medicine and combination therapies; *etc*. Retinal transplantation has a promising future due to the incorporation of current advancements and developing technologies. Researchers and clinicians can strive for more efficient and customized treatments for retinal illnesses by utilizing advancements in stem cell biology, gene editing, biomaterials, AI, and regenerative medicine.

Retinal cell transplantation still needs more investigation and optimization before aiding clinicians and surgeons with effective therapies. In the last ten years, scientific medical literature has covered this challenging field; iterations in stem cell medicine, scaffolding techniques, ophthalmic imaging, and tissue engineering will improve our knowledge of the integration between grafted and host retinal tissue. Thus, it provides hope to facilitate the visual function of patients affected by degenerative retinal diseases.

FOOTNOTES

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