The role of stem cells in the treatment of retinitis pigmentosa: contemporary insights and future perspectives

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Abstract: Retinitis pigmentosa (RP) is a hereditary degenerative disorder distinguished by the gradual deterioration of retinal pigment epithelium (RPE) cells and photoreceptors. This condition typically presents with gradual night blindness, difficulties in color perception, central vision impairment, and ultimately leads to blindness, predominantly affecting younger individuals. The irreversible loss of retinal cells poses significant challenges in the treatment of RP. Due to their distinctive potential to differentiate into various retinal cell types, stem cells have emerged as a promising therapeutic strategy for RP. Among the categories of stem cells under investigation, embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) are particularly prominent. In particular, bone marrow-derived MSCs (BM-MSCs) have shown both safety and efficacy in enhancing visual sharpness and retinal thickness in affected individuals. Moreover, recent studies have highlighted the differentiation potential of Müller glial cells into photoreceptor cells, broadening the scope for treatment. The incorporation of advanced bioengineering techniques-such as 3D bioprinting and gene editing-further enhances the prospects for innovative therapies. Despite significant progress in animal experiments and clinical trials, challenges remain, including uncertainties in cellular differentiation and complications arising from multifaceted retinal pathologies. This review aims to synthesize current insights into stem cell therapy for RP, emphasizing both achievements and ongoing challenges in the pursuit of effective treatments.

1 Introduction

Retinitis pigmentosa (RP) comprises a spectrum of inherited disorders defined by the gradual degeneration of photoreceptors and retinal pigment epithelial (RPE) cells, ultimately leading to ocular degeneration.[1] RP is a genetic disorder that affects vision, with an estimated global prevalence of approximately 1 in 4,000 individuals.[2] The onset of RP typically occurs most frequently during the teenage years, with the disease generally exhibiting a gradual progression into midlife or beyond. This degeneration of retinal functional cells results in considerable visual impairment, ultimately culminating in blindness.

RP is considered a disorder of cellular function that contributes to distinct morphological differences in the retinal structure.[3] As the disease progresses, these morphological distinctions become increasingly pronounced, which in turn adversely affects the patient's vision.[1] Although the precise pathological mechanisms underlying RP are not fully elucidated, current research indicates that the condition is associated with abnormalities in photoreceptor, alterations in cell fate, and metabolic imbalances[5]. The majority of these alterations are predominantly associated with genetic factors. Over 70 genes have been identified as related to RP, with each gene usually containing a different mutation that plays a role in the disease's etiology.[6] Noteworthy examples include PDE6 (Phosphodiesterase), CRB1 (Crumbs-homologue-1), TULP1 (Tubby-Like Protein 1), CERKL (Ceramide Kinase-Like), and RPE65 (65-kDa Retinal Pigment Epithelium), and so on. For example, the CERKL gene encodes a protein that is distinguished by the presence of ceramide kinase-like domains, potentially acting as a negative regulator of apoptosis within photoreceptor cells.[7]

Considering the relative preservation of retinal ganglion cells (RGCs) and inner retinal neurons in RP, therapeutic strategies involving transplanting cells into the subretinal compartment to facilitate their integration within the recipient retina [4]. Stem cells, recognized for their pluripotent nature and capacity for directed differentiation and proliferation, can be influenced by changes in the body's internal milieu. Such alterations activate various signaling pathways, resulting in their transformation into diverse functional retinal cell types to substitute for damaged or absent retinal cells.[8] These differentiated cells may then be injected into the vitreous body or subretinal space to substitute for injured cells and restore the normal structural integrity of the retina. Additionally, a series of experiments have demonstrated that cell therapy-based treatments can significantly improve both visual sharpness and the anatomical integrity

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of the retina in individuals diagnosed with RP.[9] An illustrative case is the clinical trial carried out by Kahraman and Oner, in which a suspension of umbilical cord mesenchymal stem cells (UCMSCs) was injected into the suprachoroidal space of 124 eyes. Over the course of a six-month follow-up, notable enhancements were observed in best-corrected visual acuity (BCVA) and retinal electrophysiological measures recordings. [10] Furthermore, stem cell therapy products designed for RP treatment have undergone rigorous clinical evaluations, substantiating their potential efficacy and safety.[11] Collectively, these results underscore the transformative promise of cell therapy in advancing RP treatment and improving patient outcomes.

2 Application of cell therapies in the treatment of RP

The non-regenerative nature of the retina, its immune-privileged properties, and its operability through surgery make stem cell therapy for RP more likely.[12] At present, various types of cells are available to treat RP, including the Müller glial cells of the adult retina [13], embryonic stem cells (ESCs) derived from the inner cell mass of the embryo, and adult stem cells (ASCs) obtained from adult tissues. Among adult stem cells, mesenchymal stem cells (MSCs) existing in human tissues and induced pluripotent stem cells (iPSCs), which exhibit properties akin to those of ESCs through in vitro reprogramming, are pivotal in the cell therapy of RP. The attributes of various types of stem cells are summarized in Table 1.

Table 1. Stem Cell Types and Characteristics

Types	source	eye differentiation	Characteristics
Müller glia cells	Extraembryonic ectoderm	RPCs, precursor rod photoreceptor cells	homeostatic regulation, metabolic support to the retina, light transmission under physiological conditions
ESCs	Early embryos or primordial germ cells	Various cell types	totipotency, pluripotency
IPSCs	Reprogrammed somatic cells	Similar to embryonic stem cells	self-renewal, differentiation capabilities
MSCs	Adult stem cells	Corneal-like cells, retinal cells	paracrine effects, anti-inflammatory, anti-apoptotic properties

RPCs, Retinal progenitor cells; ESCs, Embryonic stem cells; IPSCs, induced pluripotent stem cells; MSCs, Mesenchymal Stem Cells.

2.1 Müller glial cells

Although Müller glial cells are not traditional stem cells, they have certain stem cell properties, that is, they are mitotically active.[14] In addition, Müller glial cells in the distal retina highly express the known neural progenitor cell markers SOX2 and CHX10[15], indicating that these cells may function as retinal stem/progenitor cells (RPCs) to a certain extent.[16] Research has demonstrated that Müller glial cells can be induced to transform into post-mitotic retinal cells, such as progenitor rod cells[17] and progenitor RGCs.[18] This has been demonstrated in the eyes of P23H rat, where human Müller glial cells were transplanted and their derived photoreceptor cells migrated and integrated into the outer nuclear layer of the degenerating retina, and rod photoreceptor function was significantly improved.[17] Since Müller glial cells are obtained from the individual's own ocular tissues, this helps reduce immune rejection and provide personalized treatments, which provides a new treatment strategy for degenerative retinal diseases such as RP[13], but no results have been published on the clinical therapeutic effects of Müller glial cells (Table 2).

Table 2. Ongoing clinical trials investigating stem cell therapies for the treatment of retinitis pigmentosa

Identifier	Cell tharapy	Phase	Intervention	Recruit patients	Location
NCT03963154	hESCs-RPCs	I/II	Subretinal	12	Paris, France
NCT01736059	BMSCs	I	Intravitreal	15	California, US
NCT06242379	BMSCs	I/II	Intravitreal	15	Bangkok Noi, Bangkok, Thailand
NCT03011541	BMSCs	N/A	Retrobulbar Subtenon Intravitreal Intraocular Subretinal Intravenous	500	Westport, Connecticut, United States Coral Springs, Florida, United States Dubai, United Arab Emirates
NCT04284293	NPCs-astrocytes	I/IIa	Subretinal	16	Beverly Hills, California, United States
NCT05909488	UC-MSCs	II/III	Peribulbar	30	Yogyakarta, DI Yogyakarta, Indonesia
NCT05147701	UC-MSCs	I	Intravenous Sub-tenon	20	St. John's, Antigua and Barbuda, Buenos Aires, Argentina

					San Pedro Garza García, N.L, Mexico
NCT05786287	UC-MSCs	Obs.	N/A	18	Jakarta, DKI Jakarta/Yogyakarta, Special Region, Indonesia
NCT00874783	IPSCs	Obs.	N/A	120	Jerusalem, Israel

hESC, human embryonic stem cell; RPC, retinal pigment epithelium cell; BMSC, bone marrow mesenchymal stem cell; N/A, Not Applicable; NPC, neural progenitor cell; UC, umbilical cord; MSC, mesenchymal stem cell; Obs, Observational; IPSC, induced pluripotent stem cell.

2.2 Embryonic stem cells (ESCs)

ESCs possess extensive differentiation and proliferation potentials and can be derived into different retinal cells including photoreceptor progenitor cells and RPE cells. Research has shown that specific signaling molecules, such as retinoic acid and taurine, can substantially promote the differentiation of the progenitors into photoreceptors.[19] When these ESCs-derived neural progenitors were administered into the vitreous of mouse eyes in a model of retinal and central nervous system degeneration, the survival of photoreceptors was increased.[20] After utilizing human ESC (hESC)-derived RPE cells in the RCS rat, a famous retinal degeneration animal model, these cells survived in the mouse retina for more than 220 days, and no teratomas/tumors were found under the microscope during long-term tracking. It can be led to the conclusion that hESCs represent a promising and sustainable source of RPE. Recognizing this potential, the United States Food and Drug Administration (FDA) granted approval for the initiation of Phase I/II clinical trials involving stem cell therapies for human retinal diseases in 2010. The clinical trial primarily utilized RPE cells derived from hESCs, referred to as MA09-hRPE. In the study of Schwartz et al., these cells were transplanted into the subretinal space of a total of 18 cases of retinal diseases, and no notable adverse effects were observed during the average follow-up of 22 months, and in terms of effectiveness, the subjects' vision was significantly improved. These results show that MA09-hRPE cells have good safety and effectiveness in treating diseases with loss of retinal pigment epithelial cells.

2.3 Induced pluripotent stem cells (iPSCs)

IPSCs are derived from reprogrammed somatic cells. They were originally generated by Takahashi et al. by inducing mouse embryonic or adult fibroblasts with four transcription factors, Oct3/4, Klf4, Sox2, and c-Myc, under embryonic stem cell culture conditions. IPSCs exhibit growth properties akin to those of ESCs, and iPSCs are autologous cells, so they can be taken into account for the development of autologous therapies. IPSCs can also be converted into RPE cells, and after transplantation into Rpe65(rd12)/Rpe65(rd12) mice (a clinically relevant animal model of RP), electroretinograms demonstrated improved visual function during the survival of the RP mice. Studies have found that iPSCs induced from adult dsRed mouse skin fibroblasts have normal retinal physiological characteristics after differentiation, and can improve retinal function assessed by electroretinogram (ERG) after being transplanted under the retina. However, teratomas were generated following the transplantation of cells into the eyes of immunocompromised mice exhibiting retinal degeneration. Another Japanese study showed that after collecting epithelial cells from patients and converting them into RPE cells in vitro and transplanting them under the retina of patients, nucleotide variants were observed in the cells utilized for transplantation of the second patient. Therefore, the clinical trial of iPSCs was stopped after only two cases.

2.4 Mesenchymal stem cells (MSCs)

MSCs are ASCs with multipotency and self-renewal ability that can be obtained from different tissues, especially MSCs from bone marrow and adipose tissue, which can differentiate into different retinal cells. Bone marrow-derived MSCs (BM-MSCs) can differentiate into RPE cells. In conjunction, MSCs can also secrete neural factors to repair damaged retinal cells through their paracrine effects, and have the effect of inhibiting the inflammatory microenvironment. These effects make MSCs possible in both autologous and allogeneic transplantation. An experimental study showed that transplantation of rat BM-MSCs into the subretinal space can activate Müller cell differentiation and exert paracrine effects by secreting growth factors. Castanheira et al. found that following the intravitreal intervention of BM-MSCs into the eyes of rats exhibiting laser-induced retinal damage, the transplanted cells were found to persist in the retina for more than 8 weeks, and most of them were integrated into the RGC layer and the inner and outer nuclear layers. This shows that BM-MSCs have a strong potential to differentiate into retinal neurons. In a phase 1 study, 5 patients with inherited retinal dystrophies received intravitreal injections of autologous BM-MSCs transplantation injection. During the subsequent 10-month follow-up, no obvious adverse reactions to the retina were observed, and the BCVA of 4 patients improved from 1 line (BCVA before injection was 20/200 or worse). In addition, studies have shown that adult stem cells such as Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) have also shown attractive application prospects in retinal regeneration. In a phase 3 clinical study, the BCVA of patients improved, retinal thickening, and no adverse events occurred within 1 year after WJ-MSCs were transplanted into the subretinal space. Therefore, in RP, regardless of the gene mutation, WJ-MSCs are considered effective and safe.

3 Integration of cell therapy with innovative biotechnological approaches

The direct application of cell transplantation has been validated by a multitude of studies, demonstrating both feasibility and efficacy. The therapeutic effects are further enhanced when specific delivery materials are employed in conjunction with cell transplantation. Additionally, emerging biotechnological techniques have shown encouraging results in the maintenance and restoration of visual function. Techniques such as 3D bioprinting and gene editing stand out in this regard. When these advanced methodologies are integrated with cell transplantation, they hold promise for significantly improving the treatment outcomes for retinal diseases.

3.1 3D Bioprinting and Materials

Among the recent advancements in biotissue engineering technologies, 3D bioprinting (3DB) stands out as a significant innovation. This approach not only aids in faithfully replicating retinal-related structure but also enhances the development and functional recovery of cells. The technology utilizes biomaterials to achieve precise spatial arrangements in layered or geometric formats, effectively simulating extracellular matrices (ECMs) that contain diverse or specific cell types. This capability allows for the simultaneous printing of a functional retina. These biomaterials, commonly referred to as bioinks, can be formulated from polymers such as collagen, hyaluronic acid, and hydrogels. Studies have shown that fibrin hydrogels can be a promising choice for cell scaffolding. In vitro experiments indicate that fibrin hydrogels effectively support the growth of RPE, and their implantation into the subretinal space of porcine eyes has demonstrated good attachment of the neural retina after complete degradation. These scaffolding technologies provide not only essential physical support for cellular growth but also promote tissue repair by facilitating metabolic cooperation among cells. For instance, mitochondrial transfer from induced pluripotent stem cells has been proven to reduce mitochondrial dysfunction in PC12 cells under hypoxic-ischemic conditions. This scaffold technology offers a critical three-dimensional architecture while creating an environment that fosters the differentiation and functional maturation of stem cells. This dual functionality provides a fundamental rationale for the use of 3DB in disease modeling (see Figure 1). A notable illustration of this is the utilization of 3DB technology to create a 3D blood-retina barrier (BRB) tissue model, which facilitates a comprehensive examination of the BRB's involvement in retinal degenerative diseases.

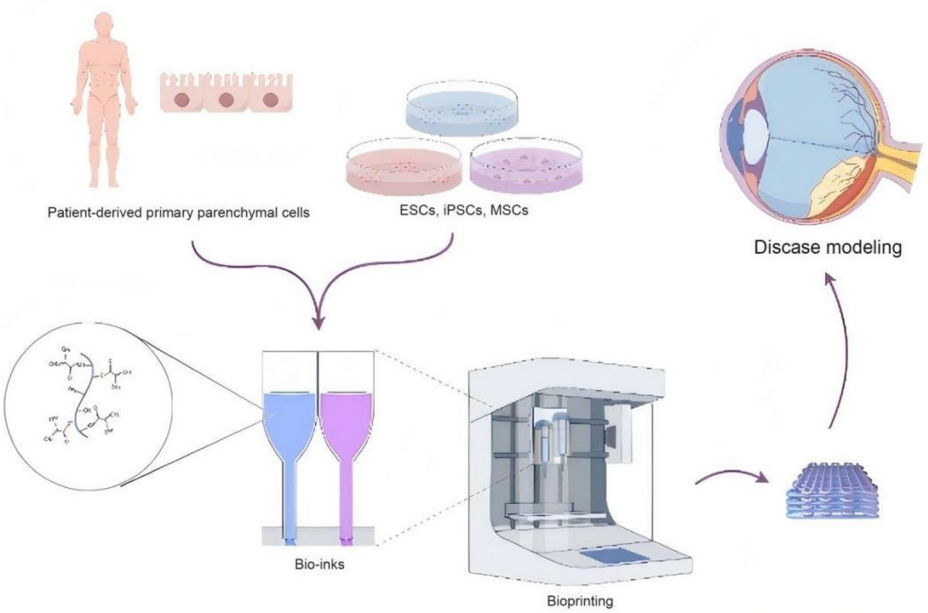

Figure 1. Schematic Overview of the 3D Printing Process.

An assortment of biological materials, encompassing patient-derived primary parenchymal cells and multiple stem cell types—including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs)—can be effectively combined with bio-printing inks. A prominent component of these inks is Gelatin methacryloyl (GelMA). By employing 3D bioprinting technology, researchers can fabricate three-dimensional structures that serve as valuable tools for disease modeling.

The structural diagram of GelMA is adapted from Zhu et al., 2024; Licensed under CC-BY.

3.2 Gene editing

The rapid development of CRISPR gene editing technology, especially in the context of establishing

disease models and treating genetic disorders, underscores its remarkable potential and expansive application opportunities. In the domain of cell therapy, the CRISPR/Cas9 system has gained significant attention for its ability to perform efficient and precise gene manipulations. This is particularly pertinent in addressing hereditary diseases like RP, where CRISPR technology could provide a viable treatment option. Furthermore, some researchers emphasize that chemical tools may play a crucial role in advancing therapies based on the CRISPR system. By enabling alterations to pathogenic gene sequences, the utilization of CRISPR/Cas9 holds promise for the potential cure of genetically induced RP. Prior research has demonstrated the application of CRISPR/Cas9 technology to edit gene structures, such as exons and introns, for the purpose of correcting autologous human iPSCs (hiPSCs) in the management of Leber's congenital amaurosis (LCA). A recent investigation successfully employed CRISPR/Cas9 to reprogram fibroblasts derived from patients with CRB1 gene mutations into iPSCs. Although the subsequent outcomes are still under examination, this work provides a crucial foundation for developing retinal organoids from iPSCs intended for individuals affected by RP associated with CRB1 gene mutations.

Furthermore, exosomes derived from stem cells have become a significant area of interest within acellular therapeutic strategies. These exosomes act as mediators of cellular signaling by transporting beneficial biomolecules that aid the restoration and rejuvenation of injured tissues. This innovative approach expands the role of scaffolding technology beyond mere physical support, transforming it into a versatile platform with multifunctional applications.

4 Challenges of Cell Therapy in the Practical Application for RP

Current treatment approaches for RP encompass a variety of methodologies; however, these strategies often face challenges in terms of their effectiveness and applicability. Cell therapy, an innovative technique, has demonstrated considerable potential in the management of RP. Nonetheless, it is confronted with several significant challenges. Key issues such as the duration of therapeutic effects, long-term safety, and reproducibility of clinical outcomes have not been adequately substantiated. Additionally, the efficiency of cell survival, integration, and functionality following transplantation remains limited, necessitating further investigation in future research.[5] Moreover, there is ongoing debate surrounding the selection of appropriate cell sources and types, transplantation techniques, immune rejection responses, and the regulation of cellular function post-transplantation. These factors are crucial determinants influencing the future development of cell therapy and its chances of clinical success. The use of stem cell therapies based on ESCs continues to evoke controversy due to concerns regarding their derivation from embryos, difficulties in controlling post-transplant cell fate, and the elevated risk of tumor formation. The transplantation of host Müller cells is associated with a low incidence of tumor formation; simultaneously, issues regarding the localization of these cells pose challenges to the direct implementation of gene editing techniques. To circumvent this issue, transplantation strategies may explore the use of Müller cells from alternative species, as these cells are capable of recognizing both apical and basal sites, which facilitates their integration into the host retina. However, the potential for immune rejection or insufficient genetic coding in the transplanted cells may limit the effectiveness of this approach. Additionally, when combining stem cell therapy with gene editing, the preservation of targeted gene modification remains a critical concern. This issue could potentially be addressed by utilizing specific Cas proteins for accurate targeting. Nevertheless, the prolonged presence of these Cas proteins within tissues raises concerns about the potential for eliciting immune responses, thereby necessitating careful consideration in their application.

5 Conclusions and perspectives

Substantial progress has been achieved in the domain of cell therapy, particularly in research focused on RP. This approach is being explored as a promising alternative to traditional treatments, especially for cases involving irreversible damage to photoreceptor cells. The pluripotency and therapeutic potential of stem cells—characterized by their widespread distribution, immune evasion capabilities, self-renewal, multipotent specialization, and release of various anti-inflammatory, immunomodulatory, or neuroprotective factors—offer renewed optimism for addressing previously intractable forms of RP. In the context of cell therapy for RP, stem cells can serve either to replace damaged retinal cells or to deliver protective factors to compromised tissues. However, without prior in vitro induction, stem cells exhibit limited efficacy in integrating or differentiating into retinal cells, primarily due to challenges associated with maintaining the integrity of the retinal barrier. Although some stem cell populations exhibit photoreceptor phenotypes, compelling evidence for synaptic integration with damaged neural cells remains lacking. Concurrently, a expanding body of literature indicates that paracrine signaling serves as a vital mechanism in stem cell transplantation, demonstrating advantageous effects on retinal tissue regeneration and functionality maintenance through the secretion of cytokines, intercellular interactions, and the release of extracellular vesicles. As an emerging field of research, stem cell-derived extracellular vesicles—particularly exosomes—hold substantial promise for acellular therapies targeting retinal dysfunction, presenting a safer and more manageable alternative to conventional cell replacement strategies. However, before fully capitalizing on their potential, further investigation is necessary to clarify the biological characteristics, therapeutic mechanisms, long-term safety, efficacy, and the inherent limitations and complexities associated with stem cell-based approaches.

Currently, while cell therapy exhibits considerable potential in clinical applications, there remains a

significant paucity of data concerning its safety and long-term effects. To address these gaps, it is essential to undertake further preclinical and clinical studies aimed at evaluating potential adverse reactions, immune rejection responses, and overall long-term safety. Equally important is the optimization of cell delivery techniques, as effectively administering cells to damaged retinal regions poses a notable challenge in the implementation of these therapies. Research efforts should prioritize the advancement of efficient and precise cell transport mechanisms that enhance both cell viability and targeting accuracy.

Additionally, the investigation of novel cell sources merits attention. Given that existing cell therapies primarily utilize stem cells—such as MSCs or iPSCs—future research could focus on identifying more effective and readily accessible cell types with improved regenerative potential. Furthermore, the integration of gene editing technologies presents a promising avenue for achieving positive therapeutic outcomes. Advances in gene editing tools, such as CRISPR/Cas9, provide new possibilities for addressing the underlying causes of diseases. Therefore, it is advisable to combine cell therapy with gene editing techniques to specifically target genetic defects. For instance, gene therapy can be employed to rectify genetic anomalies, while stem cell therapy may replace damaged cells, and pharmacological interventions can optimize the cellular microenvironment, thereby enhancing cell survival and facilitating functional recovery.

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