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REVIEW

Huang et al: Stem cell therapies for IRDs

Stem cell–based therapies for inherited retinal diseases – Translational advances and clinical evidence: A review

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ABSTRACT

Inherited retinal diseases (IRDs) represent a genetically diverse group of disorders that result in the progressive degeneration of photoreceptors and/or retinal pigment epithelium (RPE), ultimately leading to significant vision loss and diminished quality of life. Symptoms vary widely, encompassing night blindness, peripheral vision loss, central vision impairment, and total blindness, with disease progression influenced by the specific genetic mutation and inheritance pattern. This narrative review synthesizes recent findings on the pathogenesis of IRDs and examines stem cell-based interventions across preclinical models and early clinical trials. Mutations in genes such as *RPE65*, *ABCA4*, and *USH2A* disrupt critical retinal pathways, contributing to oxidative stress, inflammation, and apoptosis. Stem cell strategies, including pluripotent stem cell-derived RPE/photoreceptor precursors, mesenchymal stem cells, and retinal progenitor cells, offer potential mechanisms for limited cellular replacement and synaptic integration, as well as paracrine neuroprotection and immunomodulation. Current research indicates feasible delivery methods (intravitreal, subretinal, or suprachoroidal) with generally acceptable safety profiles; however, functional improvements in vision are often inconsistent and temporary, and durable vision restoration remains unproven. Significant challenges persist, including immune rejection, tumorigenicity risks, weak engraftment, technical complexity, and regulatory barriers. These issues underscore the necessity for standardized manufacturing processes and well-controlled, long-term clinical trials to advance the field of IRD treatment.

Keywords: Cell replacement, gene editing, immunomodulation, retinal degeneration, retinal pigment epithelium.

INTRODUCTION

Inherited retinal diseases (IRDs) cause progressive degeneration of photoreceptors or retinal pigment epithelium (RPE), leading to loss of vision. They affect approximately 1 in 4,000 individuals worldwide, with retinitis pigmentosa (RP) being the most common subtype [1, 2]. There are approximately 300 associated genes identified for IRDs and this represents a genetically diverse group of disorders. This has a severe impact on the quality of life (QoL) of an individual leading to progressive loss of vision with social, psychological, and financial limitations [1]. These cause impairment in the independence, work opportunities, and routine lives of an individual. It is documented that more than 270 genes are associated with the pathophysiology of IRDs. These have led to structural and functional alterations in the retina that complicate disease progression [2]. The inheritance patterns of IRDs (X-linked, autosomal dominant, or autosomal recessive) have specific implications for family planning, genetic counseling, and diagnosis [2, 3]. Accurate diagnosis and customized treatment plans are especially difficult due to genetic diversity and individual differences in the onset. The degradation of rod photoreceptor leads to RP with impairment of night vision and peripheral vision initially, followed by central vision loss and blindness [1]. A severe IRD known as Leber congenital amaurosis (LCA) first appears in infancy and causes blindness or early-onset visual impairment. Stargardt disease (STGD) primarily affects the macula and leads to a gradual loss of central vision [1, 2]. The present review elucidates the most recent studies and evidence on stem cell–based interventions in IRDs and describes their pathogenesis, disease progression, therapeutic mechanisms, and investigational protocols.

Molecular pathogenesis of IRDs

The molecular pathogenesis of IRDs involves a wide spectrum of gene mutations that disrupt retinal cell function and survival. Mutations in genes like RPE65, ABCA4, and USH2A impair vital biological pathways such as the visual cycle, photoreceptor renewal, and cellular structure maintenance [1, 2]. RPE65 mutations disrupt the conversion of all-trans-retinyl esters to 11-cis-retinol, a major step in phototransduction, leading to photoreceptor cell death [1, 4]. ABCA4 mutations hinder the clearance of toxic bisretinoids in the RPE, resulting in oxidative stress and lipofuscin accumulation (Figure 1) [2, 5, 6]. These molecular insults drive inflammation, mitochondrial dysfunction, and apoptotic cascades, particularly in the

RPE and photoreceptors [3, 7, 8]. USH2A mutations are associated with Usher syndrome, where defective extracellular matrix (ECM) proteins contribute to dual sensory loss involving the retina and cochlea [2, 7, 9]. Disrupted proteostasis, impaired autophagy, and glial activation further cause retinal degeneration [4, 10]. Optical coherence tomography (OCT) often shows thinning of the outer nuclear layer and RPE, aligning with disease progression [4]. A comprehensive understanding of these mechanisms is vital for tailoring gene and cell-based interventions, leading to more accurate, mutation-specific therapeutic strategies [6, 8, 11].

Clinical progression and manifestations of IRDs

IRDs show different visual symptoms, ranging from mild night blindness to complete vision loss with their severity and progression depending on genetic mutations. Early signs typically include nyctalopia, slow dark adaptation, and peripheral field defects affecting vision[8]. Patients may experience tunnel vision, loss of color discrimination, and primary vision loss with the progression of the disease, thus affecting the daily functioning and quality of life [12]. Some of the classic ophthalmoscopic features of RP are bone spicule pigmentation, attenuation of retinal vessels, and waxy pallor of the optic disc [13]. The rate of degeneration varies, even within families, emphasizing the genetic heterogeneity and phenotypic variability of IRDs [8]. Some subtypes, like Usher syndrome, involve syndromic features like sensorineural hearing loss, which complicates the diagnosis and management [12]. Thus, proper diagnosis and disease staging using multimodal imaging and genetic testing are essential to decide the prognosis and therapeutic approaches, particularly with emerging gene and cell-based interventions [8, 12, 13].

Stem cells in retinal therapy

Stem cell-based treatments target degenerative retinal disorders, including RP, and other IRDs. Studies have examined embryonic, induced pluripotent, mesenchymal, and retinal progenitor cells (RPCs) for their capability to restore retinal structure and function.

Embryonic stem cells (ESCs)

The inner cell mass of the blastocyst produces pluripotent embryonic stem cells (ESCs), which can differentiate into photoreceptors and RPE cells. Several methods

have been developed to direct ESCs toward RPE differentiation which are essential for maintaining retinal homeostasis and supporting photoreceptor survival, thus making them a primary source for retinal regeneration [6, 14, 15]. ESC-derived RPE cells have shown structural integration and sustained survival with enhanced visual acuity in various studies and trials. However, challenges including tumorigenicity, ethical concerns over embryo use, and the risk of immunological rejection often necessitate specific immunosuppressive treatments. Thus, this limits the extensive application of ESC-derived therapies [6] [9] [16, 17].

Induced pluripotent stem cells (iPSCs)

Adult somatic cells, like skin fibroblasts, can be reprogrammed into a pluripotent state to produce iPSCs. This method lowers the likelihood of immunological rejection and steers clear of moral dilemmas associated with embryonic sources [6, 18, 19]. The ability of iPSCs to develop into photoreceptors, RPE cells, and other retinal cells supports their application in tissue engineering, drug screening, and disease modelling [6, 14, 16, 18]. The feasibility and preliminary safety of clinical studies employing iPSC-derived RPE sheets for RP have been established [6, 12, 19].

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs), derived from bone marrow, adipose tissue, and the umbilical cord, have paracrine and immunomodulatory qualities that help preserve the retina. Several neurotrophic factors are produced that promote tissue repair, reduce inflammation, and increase the survival of retinal cells [20-24]. Numerous early-phase clinical trials in RP and optic neuropathies have validated MSCs' safety and showed modest improvement in visual function, even though they do not develop into retinal-specific cells [21, 23, 25]. However, their low structural integration and restricted specificity for retinal lineages suggest that their therapeutic function is mainly mediated through trophic support rather than direct cellular replacement [16, 20, 21].

Retinal progenitor cells (RPCs)

Retinal progenitor cells, arising during retinal development, differentiate into retinal neurons such as photoreceptors and interneurons [7, 9, 16, 24, 26]. Due to their developmental commitment to retinal lineages, RPCs offer a more targeted approach for retinal cell replacement, with a lower risk of tumor formation compared to

pluripotent stem cells. Preclinical studies and early human trials have shown that transplanted RPCs can survive, migrate, and integrate into the degenerating retina, partially restoring visual function. These cells have been studied in clinical trials for inherited retinal dystrophies [7, 13, 16, 26]. ESC- and iPSC-derived RPE cells have shown sustained survival and functional improvement in these models [6, 15, 19]. MSCs exhibit neuroprotective effects in RP and diabetic retinopathy via anti-inflammatory and paracrine actions [21, 23, 27]. RPCs and neural stem cells demonstrate potential in photoreceptor rescue and visual function restoration in both preclinical and clinical cases [7, 13, 26]. Emerging strategies, including stem cell-derived secretomes, biodegradable scaffolds, and gene correction technologies, aim to enhance therapeutic outcomes [27-30], therefore facilitating better clinical application. Intravitreal injection of autologous bone marrow or mesenchymal stem cells has been investigated in RP and IRDs. However, variable outcomes and complications like epiretinal membrane formation have been observed [31-36]. Transplantation of stem cell-derived RPE sheets, using scaffolds or as monolayers, has shown promising results in STGD, with improved survival and partial vision restoration [17, 19, 25]. The combination of gene correction with stem cell therapy, especially using iPSCs, provides a targeted approach for genetic retinal diseases such as RP, choroideremia, and Stargardt disease [12, 13, 19, 28]. The advances in delivery systems and biomaterials are have improved the cell survival, integration, and therapeutic efficacy in retinal regenerative medicine.

Current management challenges and the promise of stem cell therapies for IRDs

There are currently few therapeutic alternatives available for IRDs, and no widely accepted curative therapies exist. Though they are frequently mutation-specific and only work in the early stages, gene therapy and retinal prosthesis can restore some vision or delay the course of illness. Photoreceptors and RPE cells typically suffer from substantial irreparable damage by the time of diagnosis. This leads to difficulty in the treatment procedure and thus reduces therapeutic efficacy [13]. It has been observed that although there are advanced assistive technologies, there is functional blindness, particularly with respect to central and night vision, in many cases [10]. Therefore, stem-cell-based therapy has strong potential to restrict the disease progression, replace lost retinal cells, and differentiate into RPE, and ganglion cells [8,

9]. Some advanced technologies like gene editing and personalized medicine have improved the therapeutic potential of stem cell modalities [11]. There are customized treatments which can target specific genetic mutations and improves the efficiency and reduce risks, although certain limitations with respect to safety and accessibility persist [5, 6]. Newer innovations, including paracrine and secretome-based therapies, delivers neuroprotective and anti-inflammatory benefits in conditions like RP and glaucoma [27, 29, 33]. Multiple phase I/II trials have reported preliminary safety and efficacy results [11, 37-39], but challenges like immune rejection, tumorigenicity, and regulatory complexities restrict the extensive usage [16, 37, 40-42].

Scaffold-based approaches for retinal cell transplantation

One of the major drawbacks in stem cell therapy for IRDs is the limited survival and irregular incorporation of transplanted cells when they are delivered as suspensions. Biodegradable scaffolds that are constructed to mimic Bruch's membrane provide a stable surface for organized RPE monolayers and improve the graft retention and directional trophic support after subretinal placement [17]. Parylene and gelatin-based matrices produce better photoreceptor preservation than delivering cells as a free suspension [6]. The use of scaffold has increased the surgical demands and could trigger inflammatory reactions owing to the breakdown of the material [17]. Cell suspensions allow less invasive delivery through intravitreal or suprachoroidal routes but often lead to poor engraftment, cell clustering, and inadequate functional recovery [6]. Hence, the scaffold-supported delivery provides a more organized possibility for retinal repair.

Mechanisms of stem cell action in retinal diseases

Stem cell-based therapies function through multiple interconnected mechanisms, primarily involving cell replacement, paracrine signaling, immunomodulation, and restoration of synaptic connectivity (Figure 2). These mechanisms help to slow the progression of the disease and may restore visual function in patients with retinal degeneration. In retinal stem cell therapy, transplanted stem cells replace the lost photoreceptors and RPE cells by engrafting into degenerated retinal layers. Preclinical and early-phase clinical studies have shown that hESC-derived RPE cells can survive, migrate, and integrate into the subretinal space, representing native RPE cells, both

morphologically and functionally [31, 40, 43]. Photoreceptor precursors from iPSCs or RPCs incorporated into the outer nuclear layer and expressed mature photoreceptor markers [20, 34]. These findings show the capacity of stem cell therapy to restore retinal structure and function in dystrophies.

Stem cells also provide paracrine and trophic support by releasing neuroprotective factors that promote retinal cell survival and slow degeneration. MSCs secrete major cytokines and growth factors, like brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF), and pigment epithelium-derived factor (PEDF) [5, 6, 26]. These molecules help to maintain retinal structure, protect host photoreceptors, and regulate the surrounding microenvironment. In retinal degeneration models, these paracrine effects have correlated with delayed photoreceptor loss and improved retinal function, as can be observed in enhanced electroretinogram (ERG) responses [32, 44].

Stem cells, like MSCs, have immunomodulatory properties which are essential in retinal therapies. They help to suppress chronic retinal inflammation (a common feature in degenerative and autoimmune retinal diseases). MSCs secrete anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which inhibit pro-inflammatory responses and promote immune tolerance [15, 26]. Moreover, stem cells reduce microglial activation and inhibit the infiltration of immune cells into retinal tissue, thereby preventing further immune-mediated neuronal damage [45]. This aspect is particularly relevant in autoimmune uveitis and RP, where inflammation exacerbates photoreceptor loss.

The restoration of synaptic connectivity is another important mechanism. Grafted cells must survive, integrate, and form appropriate synaptic connections with existing retinal neurons to make stem cell therapies functionally effective. Experimental models have demonstrated that transplanted photoreceptors can form synaptic structures with host bipolar and horizontal cells, suggesting the possibility of re-establishing disrupted visual circuits [20, 43]. Complete functional restoration is still a challenge, but ongoing advances in stem cell differentiation protocols and transplantation techniques have improved the efficacy of synaptic integration. Hence, future success depends on refining these mechanisms, ensuring safety, and improving the delivery prospect to achieve effective clinical translation and vision restoration.

Routes of stem cell delivery in retinal diseases

Various delivery techniques have been studied depending on the target retinal layer and disease pathology. These techniques have specific advantages and disadvantages with relation to cell survival, integration, surgical feasibility, and possible complications. Table 1 provides a comparative overview of the primary delivery approaches used in clinical and preclinical settings.

Preclinical studies and animal models

Preclinical animal studies evaluate the safety and efficacy of retinal cell transplantation for IRDs. Rodent models, like rd1 and rd10 mice, along with non-human primates, effectively replicate degenerative retinal changes in IRDs [14, 22, 39, 47, 48]. These models help to study the donor cell behavior, including survival, migration, and integration into the host retina. Genetically engineered models replicating specific mutations in human IRDs improve the translation of preclinical findings and strengthen the development of targeted therapeutic approaches[14, 22, 24, 49]. Transplantation studies in these animal models have shown positive results like restoration of visual acuity and functional improvements [22, 39, 48, 50]. Donor cell survival, migration, and partial synaptic integration with host retinal circuits have been demonstrated by histological and molecular analyses thus proving the functional integration [13, 39, 48]. A number of preclinical studies used well-differentiated human pluripotent stem cell–derived retinal cells, such as hESC- or iPSC-RPE or photoreceptor precursors, transplanted into immunodeficient or immunosuppressed rodent models (rd1 or rd10 mice) to evaluate safety and survival, with follow-up periods of 6 to 12 months [14, 39, 49]. The grafts required systemic immunosuppression, for example with tacrolimus or cyclosporine, to prevent rejection, and no teratoma formation was observed [14, 49]. A separate approach with mesenchymal stem cells in immunocompetent models showed minimal immune response and no need for immunosuppression due to their low MHC class II expression and immunomodulatory properties [20, 23]. These results support short- to medium-term graft viability, though challenges such as immune compatibility, retinal remodeling, and incomplete disease modeling remain [12, 24, 39]. Refinement of models, graft preparation, delivery, and immunomodulation is needed for clinical use [14, 49].

Clinical trials and translational progress

Clinical translation of retinal cell therapies for IRDs has advanced notably, with key trials confirming safety and potential efficacy. Human embryonic stem cell-derived RPE (hESC-RPE) and induced pluripotent stem cell-derived RPE (iPSC-RPE) studies show promising outcomes (Table 2). U.S.-based Advanced Cell Technology (now Ocata Therapeutics) and Japan's RIKEN Center focused on STGD, demonstrating that subretinal RPE cell delivery is feasible, well-tolerated, and achieves encouraging anatomical improvements, supporting further clinical development [7, 22, 33, 39]. Moreover, MSC-based therapies have been evaluated for RP and STGD, with intravitreal, subtenon, and suprachoroidal injections showing positive results [33, 39]. The source of MSCs and delivery route, particularly suprachoroidal injection of umbilical cord-derived MSCs, were key factors in therapeutic efficacy [38,40]. Adverse events were mainly localized ocular issues with minimal systemic effects, supporting the safety of these approaches [22, 30, 33].

Regulatory, ethical, and technical challenges

The U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), Central Drugs Standard Control Organization (CDSCO), and Pharmaceuticals and Medical Devices Agency (PMDA) are among the organizations that help to monitor the treatments for IRDs. They require thorough clinical trials, Good Manufacturing Practices (GMP), and full cell traceability to guarantee safety and effectiveness [5, 11, 46]. Among the ethical issues surrounding embryonic stem cells (ESCs) are worries about informed consent, particularly for disadvantaged groups, and the risks associated with unlicensed stem cell clinics providing risky therapies [8, 9]. Access is further restricted by high expenses associated with stem cell manufacture, storage, and testing, especially in low-income areas, which exacerbates healthcare inequities [6, 46]. There are still unresolved technical issues with graft rejection, immunological incompatibility, post-transplant cell survival, large-scale multiplication, and cell purification [2, 5, 8]. Moreover, logistical obstacles and the lack of standardized surgical techniques prevent widespread clinical use. However, there may be answers in novel ways, such as CRISPR/Cas9 gene editing, 3D bioprinting for retinal restoration, and AI-driven therapeutic optimization. Genetic profiling-based

personalized treatment may further improve therapeutic effectiveness and equality in IRD care.

Future directions and barriers to clinical adoption

Stem cell therapy for IRDs have certain challenges prior to routine clinical use. Few of them are the high manufacturing costs and the absence of unified protocols for cell differentiation, preparation, and delivery. The risk of immune rejection and the huge variation in regulatory requirements across regions is also a major concern. There is an increasing number of unregulated clinics which are providing unproven interventions, thus causing deleterious effects to the patient confidence, and eventually reduces the responsible progress. Progress in this field depends on appropriate GMP-level manufacturing, constant functional evaluations, patient-reported measures, and better coordination between regulatory systems. The ongoing research is concentrating on allogeneic iPSC-RPE and MSC preparations and approaches that use biomaterials to support graft survival, and methods which pair gene repair with cell-based replacement. Hence, the realization of the therapeutic prospects of stem cell–based approaches will depend on controlled clinical validation, standardized procedures, and proper patient-centered results.

CONCLUSION

IRDs lead to progressive, permanent vision loss, and no curative treatment is widely available. Early human studies using MSCs, RPCs, or pluripotent-derived RPE cells show that these therapies can be delivered safely via intravitreal, subretinal, or suprachoroidal routes, even in advanced disease. Some participants have shown temporary improvements in visual function, measured by BCVA, visual fields, or electrophysiology, but these effects are uncertain, varying, and not reproducible. Most evidence are derived from small, early-phase trials without any control group and with variability in cell sources, preparation, delivery, and outcomes which restricts the interpretation. The proposed mechanisms including paracrine signaling, immunomodulation, or limited cell integration, could lead to neuroprotection; however, permanent retinal cell replacement or functional restoration has not been attained. Therefore, large, well-controlled trials with prolonged follow-up are necessary to determine the therapeutic potential in IRDs.

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REFERENCES

1.Pontikos N, et al. Genetic basis of inherited retinal disease in a molecularly characterized cohort of more than 3000 families from the United Kingdom. Ophthalmology. 2020;127(10):1384–1394.
https://doi.org/10.1016/j.ophtha.2020.04.008

2.Schneider N, et al. Inherited retinal diseases: linking genes, disease-causing variants, and relevant therapeutic modalities. Prog Retin Eye Res. 2022;89:101029.
https://doi.org/10.1016/j.preteyeres.2021.101029

3.Georgiou M, Fujinami K, Michaelides M. Inherited retinal diseases: therapeutics, clinical trials and end points–A review. Clin Exp Ophthalmol. 2021;49(3):270–288.
https://doi.org/10.1111/ceo.13917

4.Singh R, Cuzzani O, Binette F, Sternberg H, West MD, Nasonkin IO. Pluripotent stem cells for retinal tissue engineering: current status and future prospects. Stem Cell Rev Rep. 2018;14(4):463–483.
https://doi.org/10.1007/s12015-018-9802-4

5.Terrell D, Comander J. Current stem-cell approaches for the treatment of inherited retinal degenerations. Semin Ophthalmol. 2019;34(4):287–292.
https://doi.org/10.1080/08820538.2019.1620808

6.Hosseini Shabanan S, Seyedmirzaei H, Barnea A, Hanaei S, Rezaei N. Stem cell transplantation as a progressing treatment for retinitis pigmentosa. Cell Tissue Res. 2022;387(2):177–205.
https://doi.org/10.1007/s00441-021-03551-3

7.He Y, et al. Recent advances of stem cell therapy for retinitis pigmentosa. Int J Mol Sci. 2014;15(8):14456–74.
https://doi.org/10.3390/ijms150814456

8.Chen X, Xu N, Li J, Zhao M, Huang L. Stem cell therapy for inherited retinal diseases: a systematic review and meta-analysis. Stem Cell Res Ther. 2023;14(1):286.
https://doi.org/10.1186/s13287-023-03526-x

9.Galvin O, et al. The impact of inherited retinal diseases in the Republic of Ireland (ROI) and the United Kingdom (UK) from a cost-of-illness perspective. Clin Ophthalmol. 2020;14:707–719.
https://doi.org/10.2147/OPTH.S241928

10.Ahmed I, Johnston RJ Jr, Singh MS. Pluripotent stem cell therapy for retinal diseases. Ann Transl Med. 2021;9(15):1279.
https://doi.org/10.21037/atm-20-4747

11.Alcalde I, et al. Human stem cell transplantation for retinal degenerative diseases: where are we now? Medicina (Kaunas). 2022;58(1):102.
https://doi.org/10.3390/medicina58010102

12.Sen S, de Guimaraes TAC, Filho AG, Fabozzi L, Pearson RA, Michaelides M. Stem cell-based therapies for retinal diseases: focus on clinical trials and future prospects. Ophthalmic Genet. 2024:1–14.
https://doi.org/10.1080/13816810.2024.2423784

13.Uyama H, Mandai M, Takahashi M. Stem-cell-based therapies for retinal degenerative diseases: current challenges in the establishment of new treatment strategies. Dev Growth Differ. 2021;63(1):59–71.
https://doi.org/10.1111/dgd.12704

14.Wang Y, Tang Z, Gu P. Stem/progenitor cell-based transplantation for retinal degeneration: a review of clinical trials. Cell Death Dis. 2020;11(9):793.
https://doi.org/10.1038/s41419-020-02955-3

15.Sachdeva MM, Eliott D. Stem cell-based therapy for diseases of the retinal pigment epithelium: from bench to bedside. Semin Ophthalmol. 2016;31(1–2):25–9.
https://doi.org/10.3109/08820538.2015.1115253

16.Shen Y. Stem cell therapies for retinal diseases: from bench to bedside. J Mol Med (Berl). 2020;98(10):1347–1368.
https://doi.org/10.1007/s00109-020-01960-5

17.Ben M'Barek K, Habeler W, Monville C. Stem cell-based RPE therapy for retinal diseases: engineering 3D tissues amenable for regenerative medicine. Adv Exp Med Biol. 2018;1074:625–632.
https://doi.org/10.1007/978-3-319-75402-4_76

18.Tucker BA, Mullins RF, Stone EM. Stem cells for investigation and treatment of inherited retinal disease. Hum Mol Genet. 2014;23(R1):R9–R16.
https://doi.org/10.1093/hmg/ddu124

19.Maeda A, Mandai M, Takahashi M. Gene and induced pluripotent stem cell therapy for retinal diseases. Annu Rev Genomics Hum Genet. 2019;20:201–216.
https://doi.org/10.1146/annurev-genom-083118-015043

20.Ng TK, Fortino VR, Pelaez D, Cheung HS. Progress of mesenchymal stem cell therapy for neural and retinal diseases. World J Stem Cells. 2014;6(2):111–9.
https://doi.org/10.4252/wjsc.v6.i2.111

21.Labrador-Velandia S, et al. Mesenchymal stem cell therapy in retinal and optic nerve diseases: an update of clinical trials. World J Stem Cells. 2016;8(11):376–383.
https://doi.org/10.4252/wjsc.v8.i11.376

22.Finocchio L, Zeppieri M, Gabai A, Spadea L, Salati C. Recent advances of adipose-tissue-derived mesenchymal stem cell-based therapy for retinal diseases. J Clin Med. 2023;12(22):7015.
https://doi.org/10.3390/jcm12227015

23.Holan V, Palacka K, Hermankova B. Mesenchymal stem cell-based therapy for retinal degenerative diseases: experimental models and clinical trials. Cells. 2021;10(3):588.
https://doi.org/10.3390/cells10030588

24.Chen X, Jiang Y, Duan Y, Zhang X, Li X. Mesenchymal-stem-cell-based strategies for retinal diseases. Genes (Basel). 2022;13(10):1901.
https://doi.org/10.3390/genes13101901

25.Mehat MS, et al. Transplantation of human embryonic stem cell-derived retinal pigment epithelial cells in macular degeneration. Ophthalmology. 2018;125(11):1765–1775.
https://doi.org/10.1016/j.ophtha.2018.04.037

26.Jeon S, Oh IH. Regeneration of the retina: toward stem cell therapy for degenerative retinal diseases. BMB Rep. 2015;48(4):193–9.
https://doi.org/10.5483/BMBRep.2015.48.4.276

27.Puertas-Neyra K, Usategui-Martin R, Coco RM, Fernandez-Bueno I. Intravitreal stem cell paracrine properties as a potential neuroprotective therapy for retinal photoreceptor neurodegenerative diseases. Neural Regen Res. 2020;15(9):1631–1638.
https://doi.org/10.4103/1673-5374.276324

28.Li H, Hou L. Personalized stem cell-based therapy for degenerative retinal diseases. Stem Cell Rev Rep. 2020;16(5):1013–1015.
https://doi.org/10.1007/s12015-020-10003-y

29.Usategui-Martin R, Fernandez-Bueno I. Neuroprotective therapy for retinal neurodegenerative diseases by stem cell secretome. Neural Regen Res. 2021;16(1):117–118.
https://doi.org/10.4103/1673-5374.283498

30.Liu H, et al. Towards stem/progenitor cell-based therapies for retinal degeneration. Stem Cell Rev Rep. 2024;20(6):1459–1479.
https://doi.org/10.1007/s12015-024-10740-4

31.Siqueira RC. Stem cell therapy in retinal diseases? Rev Bras Hematol Hemoter. 2012;34(3):222–6.
https://doi.org/10.5581/1516-8484.20120054

32.Garcia JM, Mendonca L, Brant R, Abud M, Regatieri C, Diniz B. Stem cell therapy for retinal diseases. World J Stem Cells. 2015;7(1):160–4.
https://doi.org/10.4252/wjsc.v7.i1.160

33.Jin N, Sha W, Gao L. Shaping the microglia in retinal degenerative diseases using stem cell therapy: practice and prospects. Front Cell Dev Biol. 2021;9:741368. https://doi.org/10.3389/fcell.2021.741368

34.Apatoff MBL, et al. Autologous stem cell therapy for inherited and acquired retinal disease. Regen Med. 2018;13(1):89–96. https://doi.org/10.2217/rme-2017-0089

35.Kim JY, You YS, Kim SH, Kwon OW. Epiretinal membrane formation after intravitreal autologous stem cell implantation in a retinitis pigmentosa patient. Retin Cases Brief Rep. 2017;11(3):227–231. https://doi.org/10.1097/ICB.0000000000000327

36.Weiss JN, Levy S. Stem cell ophthalmology treatment study: bone marrow derived stem cells in the treatment of retinitis pigmentosa. Stem Cell Investig. 2018;5:18. https://doi.org/10.21037/sci.2018.04.02

37.Rao RC, Dedania VS, Johnson MW. Stem cells for retinal disease: a perspective on the promise and perils. Am J Ophthalmol. 2017;179:32–38. https://doi.org/10.1016/j.ajo.2017.04.007

38.Han F, Xu G. Stem cell transplantation therapy for retinal degenerative diseases. Adv Exp Med Biol. 2020;1266:127–139. https://doi.org/10.1007/978-981-15-4370-8_9

39.Ajgaonkar BS, Kumaran A, Kumar S, Jain RD, Dandekar PP. Cell-based therapies for corneal and retinal disorders. Stem Cell Rev Rep. 2023;19(8):2650–2682. https://doi.org/10.1007/s12015-023-10623-0

40.Voisin A, Penaguin A, Gaillard A, Leveziel N. Stem cell therapy in retinal diseases. Neural Regen Res. 2023;18(7):1478–1485. https://doi.org/10.4103/1673-5374.361537

41.Holan V, Hermankova B, Kossl J. Perspectives of stem cell-based therapy for age-related retinal degenerative diseases. Cell Transplant. 2017;26(9):1538–1541. https://doi.org/10.1177/0963689717721227

42.Nair DSR, Thomas BB. Stem cell-based treatment strategies for degenerative diseases of the retina. Curr Stem Cell Res Ther. 2022;17(3):214–225. https://doi.org/10.2174/1574888X16666210804112104

43.Mead B, Berry M, Logan A, Scott RA, Leadbeater W, Scheven BA. Stem cell treatment of degenerative eye disease. Stem Cell Res. 2015;14(3):243–57. https://doi.org/10.1016/j.scr.2015.02.003

44.Balmer J, Stanzel BV, Fischer MD. Stem cell therapy for retinal diseases. Ophthalmologe. 2015;112(9):728–37. https://doi.org/10.1007/s00347-015-0119-2

45.Wu N, Wang Y, Yang L, Cho KS. Signaling networks of retinal ganglion cell formation and the potential application of stem cell-based therapy in retinal degenerative diseases. Hum Gene Ther. 2016;27(8):609–20. https://doi.org/10.1089/hum.2016.083

46.Avery RL, et al. Intravitreal injection technique and monitoring: updated guidelines of an expert panel. Retina. 2014;34(Suppl 12):S1–S18. https://doi.org/10.1097/IAE.0000000000000399

47.Khaboushan AS, et al. Cell therapy for retinal degenerative disorders: a systematic review and three-level meta-analysis. J Transl Med. 2024;22(1):227. https://doi.org/10.1186/s12967-024-05016-x

48.Zhao T, et al. Intravenous infusion of umbilical cord mesenchymal stem cells maintains and partially improves visual function in patients with advanced retinitis pigmentosa. Stem Cells Dev. 2020;29(16):1029–1037. https://doi.org/10.1089/scd.2020.0037

49.Radu M, Branisteanu DC, Pirvulescu RA, Dumitrescu OM, Ionescu MA, Zemba M. Exploring stem-cell-based therapies for retinal regeneration. Life (Basel). 2024;14(6):668. https://doi.org/10.3390/life14060668

50.Moghadam Fard A, Mirshahi R, Naseripour M, Ghasemi Falavarjani K. Stem cell therapy in Stargardt disease: a systematic review. J Ophthalmic Vis Res. 2023;18(3):318–327.
https://doi.org/10.18502/jovr.v18i3.13780

51.Tuekprakhon A, et al. Intravitreal autologous mesenchymal stem cell transplantation: a non-randomized phase I clinical trial in patients with retinitis pigmentosa. Stem Cell Res Ther. 2021;12(1):52.
https://doi.org/10.1186/s13287-020-02122-7

52.Kahraman NS, Oner A. Umbilical cord derived mesenchymal stem cell implantation in retinitis pigmentosa: a 6-month follow-up results of a phase 3 trial. Int J Ophthalmol. 2020;13(9):1423–1429.
https://doi.org/10.18240/ijo.2020.09.14

53.Oner A, Kahraman NS, Unal A. Evaluating the long-term efficacy of umbilical cord-derived mesenchymal stem cell therapy in retinitis pigmentosa: findings from a 1–4-year follow-up. Stem Cells Transl Med. 2025;14(8):szaf034.
https://doi.org/10.1093/stcltm/szaf034

54.Ozmert E, Arslan U. Management of retinitis pigmentosa by Wharton's jelly derived mesenchymal stem cells: preliminary clinical results. Stem Cell Res Ther. 2020;11(1):25.
https://doi.org/10.1186/s13287-020-1549-6

55.Liu Y, et al. Long-term safety of human retinal progenitor cell transplantation in retinitis pigmentosa patients. Stem Cell Res Ther. 2017;8(1):209.
https://doi.org/10.1186/s13287-017-0661-8

TABLES AND FIGURES WITH LEGENDS

Table 1. Routes of stem cell delivery for retinal regeneration: Key features, advantages, challenges, and current status

Routes	Chief features	Advantages	Challenges	Current status
Intravitreal injection	Cells injected into the vitreous cavity. Targets ganglion cell layer and inner retina.	Minimally invasive, repeatable, safe technique [27, 46].	Limited cell migration to outer retina; risk of inflammation or ERM [35].	Widely used in trials; focus on neuroprotection [13, 27, 40].
Subretinal injection	Cells delivered between neurosensory retina and RPE. Directly targets photoreceptors and RPE.	Precise delivery; promotes photoreceptor integration [6, 9, 16]	Technically demanding; retinal detachment risk; limited spread [16].	Most effective for vision restoration in RPE/photoreceptor loss [6, 7].
Suprachoroidal injection	Injection into the potential space between sclera and choroid. Targets choroid/RPE interface.	Less invasive than subretinal; wide diffusion [8, 22].	Limited human data; cell homing to retina uncertain[16, 22].	Promising preclinical and early clinical data [42].
Subtenon and epiretinal	Subtenon: under Tenon's	Experimental routes;	Inconsistent targeting;	Preclinical; not yet standard; being

	capsule; Epiretinal: on retinal surface (ILM side).	potential slow-release delivery [18]	limited cell integration; under evaluation [18, 35].	explored in select studies [18, 35, 47].

Abbreviations: BCVA: Best-corrected visual acuity; ERM: Epiretinal membrane; ILM: Internal limiting membrane; RPE: Retinal pigment epithelium.

Table 2. Summary of clinical trials on stem cell-based therapies for IRDs

Author / year	Disease	Stem cell type and dose	Delivery	Registry / phase	Sample (treated)	Key outcomes	Safety
Zhao et al. (2020) [48]	RP	UC-MSCs; 1×10^8 cells	IV	ChiCTR-ONC-16008839; I/II	32 pts (64 eyes)	Best-Corrected Visual Acuity (BCVA) gain was defined as ≥5 letters. At 12 months, 81.3% of patients maintained or improved BCVA. National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ25) scores rose at 3 months. Visual field sensitivity and Flash Visual Evoked	No serious adverse effects (SAEs); no tumorigenesis, rejection, or vascular leakage.

						Potential (FVEP) showed no change.	
Weiss et al. (2018) (SCOTS/SCOTS2) [36]	RP	Autologous BMSC (~1.2B Total nucleated cells)	Retrobulbar + Subtenon ± Intravitreal + IV	NCT01920867 / NCT03011541	17 pts (33 eyes)	Improvement was defined as a ≥1-line Snellen gain. Overall, 45.5% of eyes improved, 45.5% remained stable, and 9% worsened. Mean gain was 7.9 Snellen lines, with a 31% LogMAR improvement (P = 0.016).	No reported surgical or inflammatory complications.
Mehat et al. (2018) [25]	STGD	hESC-RPE (MA09-hRPE) 50k–200k cells	Subretinal	NCT01469832; I/II	12 pts (12 eyes)	All participants showed hyperpigmentation, indicating graft survival. No one achieved functional improvement: BCVA	No cell-related SAEs; procedure-linked events: retinal dialysis (1), subretinal hemorrhage (2), pigment dispersion

						changed ≤5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and microperimetry sensitivity showed no significant gains at 12 months. One high-dose case had localized retinal thinning with reduced sensitivity.	(4); immunosuppression AEs in 5.
Tuekprakhon et al. (2021) [51]	RP	Autologous BM-MSCs (1×10^6 / 5×10^6 / 1×10^7)	Intravitreal	NCT01531348; Phase I	14 pts	BCVA showed transient significant gains (–0.18 logMAR in 1×10^6 group at months 7–8, $p < 0.05$) but returned to baseline by 12 months. No participants	Mild transient inflammation; transient Intraocular Pressure (IOP) spikes; single cases: synechiae, Cystoid Macular Edema (CME), choroidal

						consistently met the ≥5 ETDRS letter threshold. VF and CST remained stable. Patient-reported outcomes: 50% stable vision, 35.7% improved dim-light tasks	detachment; long-term: 1 vitreous hemorrhage with osseous metaplasia (resolved).
Kahraman et al. (2020) [52]	RP	UC-MSCs; 5M cells/eye	Suprachoroidal (Limoli)	Turkish MoH 56733164/203; Phase III	124 eyes / 82 pts	Mean BCVA improved 0.27 logMAR (1.36 → 1.09). Visual Field Mean Deviation (VF MD)improved 28.12 → 24.19 dB ($P < 0.05$), and central mfERG P1 amplitudes increased. Based on BCVA changes, 46%	No major ocular/systemic issues; 1 transient vision loss episode; temporary VF defect resolved.

						improved, 42% stable, 12% worsened.	
Oner et al. (2025) [53]	RP	UC-MSCs; 5M cells/eye	Suprachoroidal	Turkish MoH 56733164/203; Phase III (long-term)	669 eyes / 429 pts	BCVA improved 0.30 logMAR at 2 years and remained +0.17 logMAR at 4 years. VF MD increased +1.36 dB at 2 years ($P < 0.05$). Central mfERG P1 amplitudes rose significantly and persisted to 4 years. FST thresholds improved at 1 year (white stimulus +9.7 dB).	No therapy-related SAEs; common: conjunctival hyperemia (67%), light sensitivity (18%). 2 myopic RD cases (not linked).
Özmert et al. (2020) [54]	RP	WJ-MSCs 2–6M cells;	Sub-Tenon (deep)	SHGM56733164; Phase III	32 pts (34 eyes)	BCVA improved 10.1 ETDRS letters (70.5 → 80.6, $p = 0.01$). VF MD	No SAEs; no inflammation, IOP rise, rejection, RD; 1

		GMP P3				improved 2.6 dB (27.3 → 24.7, p = 0.01). Outer retinal thickness increased 100 → 119 μm (p = 0.01). Central Multifocal Electroretinography (mfERG) P1 amplitude and implicit time improved (p ≤ 0.02); peripheral unchanged. Flicker ERG amplitude increased and implicit times decreased (p = 0.01).	transient nystagmus increase.
Liu et al. (2017) [55]	RP	Human fetal-derived RPCs;	Subretinal	ChiCTR-TNRC-08000193; Phase I	8 pts	BCVA improved 10.1 ETDRS letters (70.5 → 80.6, p = 0.01). VF MD increased 2.6 dB (27.3	No rejection, tumors, RD, endophthalmitis, CME. One ERM at 12 mo. Imaging stable.

		1×10^6 cells				→ 24.7, p = 0.01). Outer retinal thickness rose 100 → 119 μm (p = 0.01). Central mfERG P1 amplitude and implicit time improved ($p \leq 0.02$); peripheral unchanged. Flicker Electroretinography (ERG) amplitude increased, implicit times decreased (p = 0.01).	

Abbreviations: BCVA: Best-corrected visual acuity; VF: Visual field; FVEP: Flash visual evoked potential; NEI-VFQ25: National Eye Institute Visual Function Questionnaire-25; BMSC: Bone marrow–derived stem cells; hESC-RPE: Human embryonic stem cell–derived retinal pigment epithelium; CST: Central subfield thickness; mfERG: Multifocal electroretinography; FST: Full-field stimulus threshold; WJ-MSC: Wharton's

jelly–derived mesenchymal stem cells; ETDRS: Early Treatment Diabetic Retinopathy Study; RD: Retinal detachment; CME: Cystoid macular edema; RPCs: Retinal progenitor cells; SAEs: Serious adverse events; IOP: Intraocular pressure.

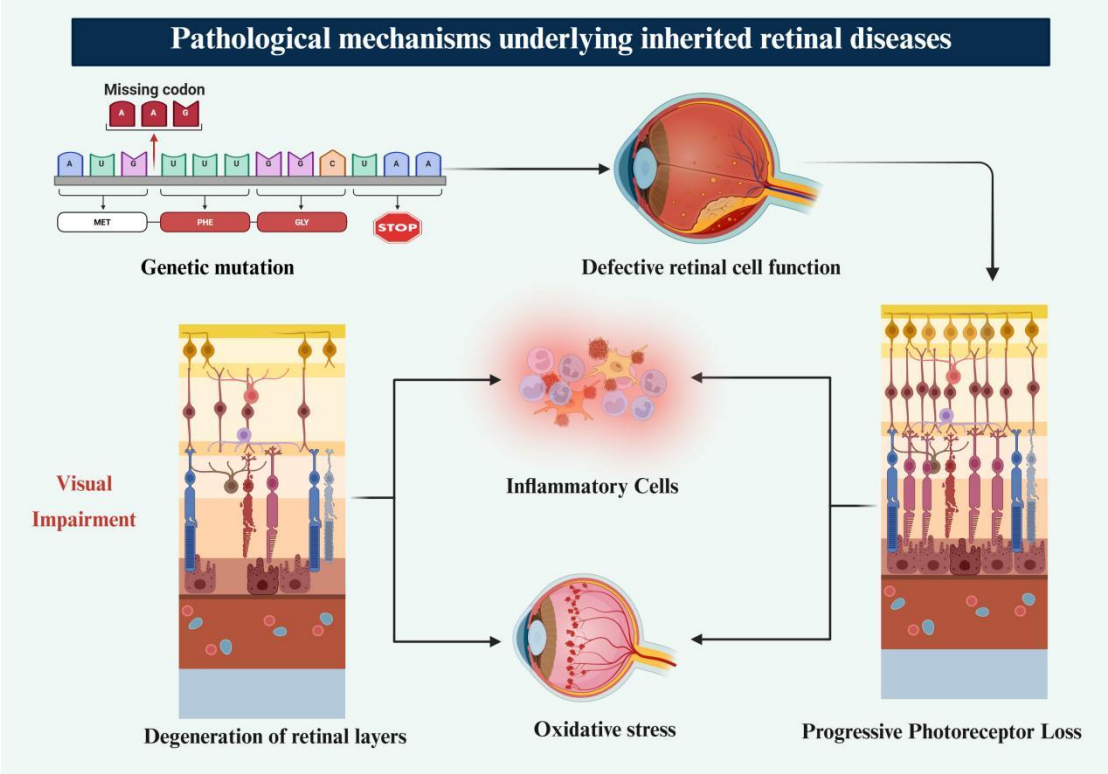

Figure 1. Pathophysiology of IRDs. Schematic overview of the disease cascade in IRDs. Primary genetic mutations impair photoreceptor and/or RPE function, promoting the accumulation of toxic by-products. These disturbances trigger OS and activation of inflammatory cells, which amplify tissue injury through a self-propagating feedback loop. The resulting milieu accelerates progressive photoreceptor loss, degeneration of retinal layers, and ultimately visual impairment. Abbreviations: IRDs: Inherited retinal diseases; RPE: Retinal pigment epithelium; OS: Oxidative stress.

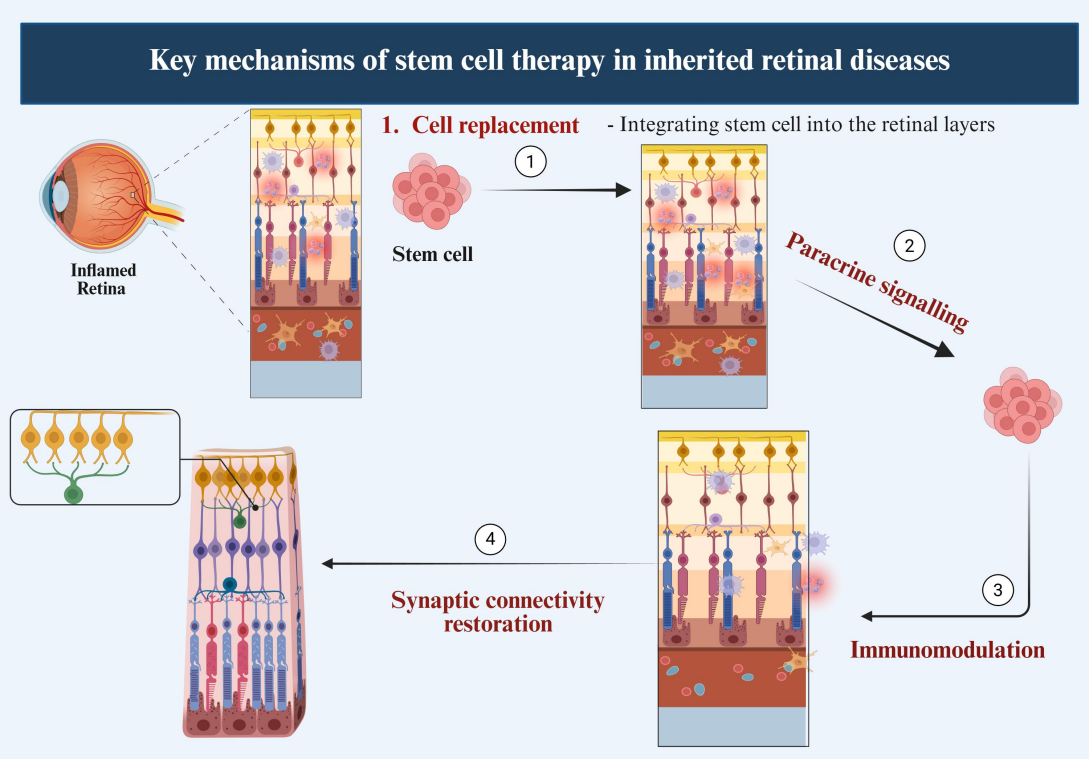

Figure 2. Mechanisms of stem cell action in IRDs. Schematic representation of the principal, interconnected pathways through which SC therapies may promote retinal repair in IRDs. (1) Cell replacement: transplanted SCs engraft within degenerated retinal layers and differentiate into retinal lineages—most notably PRs and/or RPE—to replenish lost cells. (2) Paracrine signalling: SCs release neurotrophic and cytoprotective mediators (e.g., BDNF, CNTF, GDNF, PEDF) that enhance host-cell survival, stabilize the retinal microenvironment, and attenuate OS. (3) Immunomodulation: SCs reduce chronic retinal inflammation by suppressing pro-inflammatory pathways, limiting microglial activation, and promoting anti-inflammatory cytokine signalling (e.g., IL-10, TGF-β). (4) Synaptic connectivity restoration: graft-derived PRs mature and establish synaptic contacts with host bipolar and horizontal cells, supporting reconstitution of disrupted retinal circuitry. The relative contribution of these mechanisms depends on the SC source (e.g., hESC-/iPSC-derived retinal cells, MSCs, RPCs), disease stage, and delivery context. Abbreviations: IRDs: Inherited retinal diseases; SC: Stem cell; PRs: Photoreceptors; RPE: Retinal pigment epithelium; BDNF: Brain-derived neurotrophic factor; CNTF: Ciliary neurotrophic factor; GDNF: Glial cell line-derived neurotrophic factor; PEDF: Pigment epithelium-derived factor; OS: Oxidative stress; IL-10: Interleukin-10; TGF-β: Transforming growth factor-beta; hESC: Human embryonic stem cell; iPSC:

Induced pluripotent stem cell; MSCs: Mesenchymal stem cells; RPCs: Retinal progenitor cells.