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Review Article

Review On Stem Cell Therapy for Retinal Damage

Pratiksha Kadale*[1], Sakshi Ghunake[2], Sadiya Jamadar[3], Ganesh Chavan [4]

[1,2,3]*Women's College of Pharmacy Peth Vadgao, Kolhapur, Maharashtra.*
[4]*Suyash College of Pharmacy Warud, Jalna Maharashtra.*

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ABSTRACT

Retinal damage is a leading cause of vision impairment and blindness, with limited therapeutic options available for effective restoration of vision. Stem cell therapy has emerged as a promising approach to regenerate damaged retinal tissues and restore visual function. Various stem cell sources, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and retinal progenitor cells (RPCs), have been extensively studied for their potential in treating retinal diseases such as age-related macular degeneration (AMD), retinitis pigmentosa (RP), and diabetic retinopathy (DR). Preclinical and clinical studies have demonstrated the ability of stem cells to differentiate into retinal cells, integrate into host tissue, and promote neuroprotection through paracrine effects. However, challenges such as immune rejection, tumorigenicity, ethical concerns, and controlled differentiation must be addressed to optimize the safety and efficacy of stem cell-based therapies. This review provides a comprehensive analysis of recent advancements in stem cell therapy for retinal damage, highlighting key findings from experimental and clinical studies, potential mechanisms of action, and future perspectives in the field.

INTRODUCTION

Retinal degeneration is one of the major reasons for vision loss, and stem cell Therapy has been extensively investigated to repair and regenerate damaged retinal Cells. Several types of stem cells have been tested in preclinical and clinical trials to Understand their efficiency in reversing retinal degeneration. To date, human Embryonic stem cells (HESCS)-, induced pluripotent stem cells (iPSCs)-derived RPE cells, mesenchymal stem cells (MSCs) and retinal progenitor cells (RPCs) Have been tested in addition to paracrine factors and exosomes derived from MSCs. Conventional therapies for retinal diseases slow the progression of the diseases; However, the long-term benefit is achieved by repairing and regenerating the damaged Retinal tissue. Moreover, since the retina

***Corresponding Author:** Pratiksha Kadale
Address: Women's College Of Pharmacy Peth Vadgao, Kolhapur, Maharashtra.
Email ✉: pratikshakadale19@gmail.com
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does not have intrinsic regenerative properties, Stem cell therapies have been sought to repair and regenerate the damaged retina. Several preclinical and clinical studies have demonstrated that transplantation of stem Cells and factors derived from stem cells produce clinically measurable improvement. This review will discuss the different stem cells utilized to treat retinal diseases and the Clinical benefits and challenges in utilizing stem cells to treat retinal degeneration. The etiology of retinal degenerative diseases includes genetic and non-genetic Factors leading to the loss of photoreceptor cells and eventually the RPE cells. Age-Related macular degeneration (AMD) is one of the most common forms of vision loss, which might either be due to degradation of RPE cells (dry AMD) or choroidal neovascularization (wet AMD). Retinitis pigmentosa (RP) occurs due to Autosomal4 or X-linked mutations, which contribute to the Degeneration of photoreceptors leading to vision loss Diabetic retinopathy (DR) is caused due to chronic hyperglycemia

Types Of Stem Cells In Retinal Therapy

1 Embryonic Stem Cells (ESCs)

ESCs, derived from the inner cell mass of blastocysts, have pluripotency and the ability to differentiate into retinal cells. Studies have demonstrated the successful differentiation of ESCs into retinal pigment epithelium (RPE) cells and photoreceptors, making them a valuable candidate for retinal regeneration. However, ethical concerns and the risk of tumorigenicity pose significant challenges to their clinical use.

2 Induced Pluripotent Stem Cells (iPSCs)

iPSCs, generated by reprogramming somatic cells into a pluripotent state, provide an ethical alternative to ESCs. These cells can differentiate into various retinal cell types and hold potential for patient-specific therapy, reducing the risk of immune rejection. However, challenges such as genomic instability and incomplete differentiation must be addressed before clinical translation.

3 Mesenchymal Stem Cells (MSCs)

MSCs, derived from bone marrow, adipose tissue, and umbilical cord, have immunomodulatory properties and secrete neurotrophic factors that support retinal survival. MSCs do not differentiate directly into retinal cells but exert protective effects via paracrine signaling, making them a viable option for treating inflammatory and degenerative retinal conditions.

4 Retinal Progenitor Cells (RPCs)

RPCs are neural progenitor cells capable of differentiating into retinal neurons and photoreceptors. These cells have been used in preclinical models to restore visual function, but their limited proliferation and differentiation capacity require further optimization.

Mechanisms of Stem Cell-Mediated Retinal Repair

Stem cells contribute to retinal repair through various mechanisms:

- **Cell Replacement:** Direct differentiation into retinal cells such as photoreceptors and RPE.
- **Paracrine Effects:** Secretion of neurotrophic factors (e.g., brain-derived neurotrophic factor, ciliary neurotrophic factor) that promote survival and reduce inflammation.
- **Immunomodulation:** Suppression of immune responses to reduce retinal inflammation and apoptosis.

- **Neovascularization:** Induction of controlled angiogenesis in ischemic retinal conditions.

Retinal Degeneration

The human adult retina is organized in ten histological layers with one glial Cell type, the Müller glial cells, and six major types of neurons: two main cell Types of photoreceptors (PRs; rods and cones), bipolar cells, amacrine cells, Horizontal cells, and ganglion cells. Retinal cell bodies are organized into three Layers from apical to basal; the outer nuclear layer, the inner nuclear layer, and The ganglion cell layer. Aside from these layers, the outer and inner plexiform Layers contain axons and dendrites of neuronal cells. The outer part of the Retina is limited by the retinal pigment epithelium (RPE) layer. These cells Fulfill many functions such as epithelial transport, visual cycle, phagocytosis, Secretion, and immune modulation.

1. Retinitis Pigmentosa (RP)

RP is the most frequent hereditary (30–40% autosomal dominant, 40–60% Autosomal recessive, and 5–15% X-linked) retinal disease with an incidence Of approximately 1:4000. Patients suffering from RP Frequently report night blindness and progressive visual field loss beginning Around the age of 20–30 years, and finally are complete blindness at the Late stage. The disease is characterized by primary degeneration of PR rods (eventually secondary degeneration of cones in case of complete blindness). At fundus examination, the disease is clinically characterized By dark bone-spicule pigmentation and attenuated blood vessels. RP consists of a group of inherited retinal disorders With a prevalence of approximately 1 in 4,000 people Worldwide. Patients typically present early in life, Often in the first or second decade, with progressive loss of Peripheral vision and night vision. Over time, RP progresses To central vision loss and blindness. The hallmark Clinical findings for RP include peripheral bone spicules, Optic disc pallor and attenuated retinal vessels. The Condition is inherited but the transmission can be autosomal Dominant, autosomal recessive, or X-linked recessive. To Date, mutations in more than 80 different genes involved In phototransduction cascade, ciliary transport, and ciliary Structure have been implicated in non-syndromic RP. These mutations result in the dysfunction and loss Of photoreceptor cells, and dysfunction and intraretinal Migration of RPE cells significant progress has been made in gene Supplementation for autosomal recessive and X-linked RP, and in RNA therapeutics and genome editing for Autosomal dominant RP. Although gene therapy Is an attractive therapeutic option, it is only effective In preserving or improving vision in patients without Significant photoreceptor loss in the macula, and in the Subset of cases in which the pathogenic mutation has been Identified. As such, there is great interest in the use of PSC-Derived photoreceptors in replacing the lost photoreceptors In RP in an effort to limit or reverse vision loss associated With RP. In developing autologous PSC transplantation strategies For RP and other retinal disease targets, it is important to Consider the presence of causative genetic mutations in the Donor cells. Ex vivo gene therapy to correct the genetic Defect in autologous donor cells prior to transplantation is A potential solution. This concept has been studied recently In a mouse model of RHO-related RP, wherein ex vivo Minicircle DNA vector-based gene correction of allogeneic Photoreceptor precursor cells prior to transplantation was Shown to have similar long-term therapeutic efficiency as Compared to AAV-based ex vivo correction.

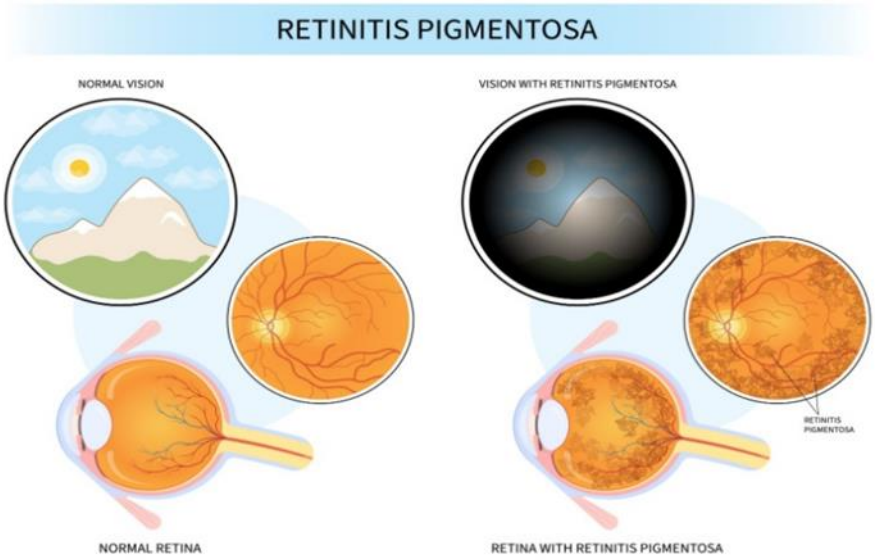

Fig.1) Disease Affected Eye and Vision of Patient

2. Age -related Macular Degeneration (AMD)

AMD is a complex multifactorial disease characterized by degeneration of the Macula usually preceded by drusen formation made up of the extracellular Accumulation of proteins and lipids. The disease usually Affects older adult individuals and is the leading cause of blindness in Industrialized countries. The pathogenesis of this retinal disease is associated With both genetic (CFH, ARMS2, etc.) and environmental factors (smoking And light exposure). AMD is classified in an atrophic form with the Progressive development of macular atrophy and an exudative form with the development of choroidal neovascularization. Both forms are clinically characterized by visual acuity decrease, central Scotoma, and metamorphopsia is the leading cause of blindness in people aged over 55 years in developed countries. Clinically, patients Typically present with late-onset progressive loss of central Vision. There are two forms of AMD. Nonexudative or Dry AMD is the more common form. It is characterized by Accumulation of subretinal deposits called drusen during the Early stages of the disease when significant vision loss has Not occurred. Progression of dry AMD is characterized By dysfunction and chronic progressive degeneration of RPE cells, which are crucial for the function and survival Of the overlying photoreceptor cells. This loss of RPE cells Leads to geographic atrophy where focal loss of overlying Photoreceptors occur. This is associated with significant Vision loss if the retina providing central vision becomes Affected. When geographic atrophy involves the central Vision, the eye has advanced non-exudative AMD and vision Loss that is not reversible. Advanced nonexudative AMD Is the specific stage of AMD that is the treatment target of RPE and/or photoreceptor cell regeneration using PSCs. Genetic and environmental risk factors are implicated In dry AMD pathogenesis and its progression from the Early to the advanced stage. Several clinical trial Aiming to halt dry AMD progression are currently on-Going (NCT03846193, NCT03144999, NCT04358471). Among the strategies under investigation is the reduction Of excessive activation of complement by C3 inhibition, A shared component of all three complement activation Pathways. No product has yet been approved for clinical use once significant

cellular has occured, Pharmacological strategies such as complement inhibition Will not be effective in restoring vision because the lost Cells cannot regenerate. PSC-based therapy may provide an Avenue for treatment at this stage. Given the localized loss Of RPE and photoreceptors in AMD, this retinal disease is a Particularly attractive for stem cell-based therapies. Only a Small focal area of cells in the macula needs to regenerate for Visual restoration or improvement to occurExudative or wet AMD, another form of advanced AMD, Accounts for 10–15% of AMD cases. In exudative AMD, Abnormal choroidal or subretinal neovascularization leads To vascular exudation and hemorrhage that compromise The function and viability of photoreceptor and RPE cells.The process is relatively acute. Although exudative AMD Is associated with greater visual morbidity, the advent of Intravitreal anti-vascular endothelial growth factor (VEGF) Therapy has significantly improved functional outcomes for Patients with exudative AMD. In general, if vascular Exudation and hemorrhage is effectively halted using Anti-VEGF therapy, then retinal cellular damage can be Minimium

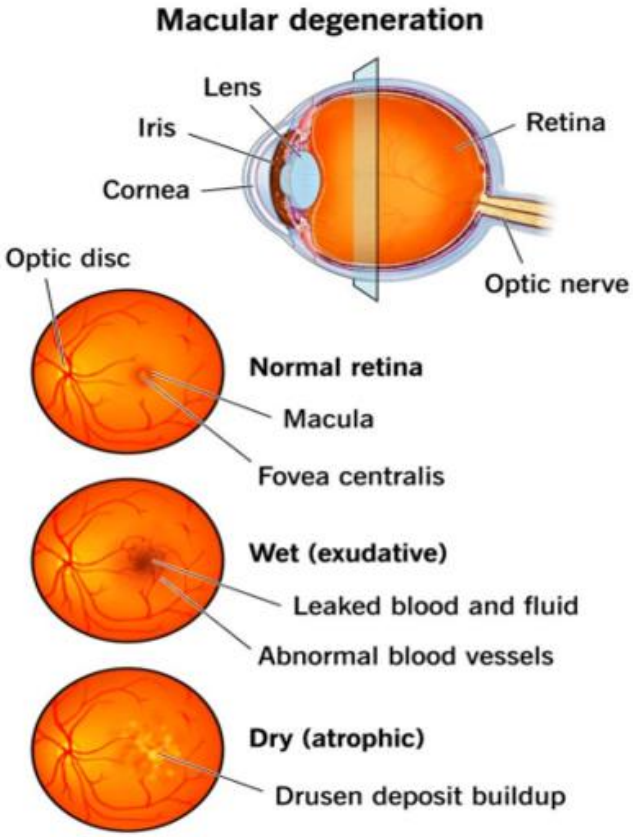

Fig.2) Disease affected eye and vision of patient

3. Recessive Stargardt Macular Degeneration

Recessive Stargardt macular degeneration (STGD1) is common retinal Dystrophy of varying severity, the most common and severe form during Childhood, and the less common form during adulthood. STGD1 is an autosomal recessive disease with an incidence of 1:8000 to 1:10,000, caused by mutations in the ATP binding cassette subfamily A Member 4 (ABCA4) gene. The Protein encoded by ABCA4 is involved in the visual cycle and localized in the Photoreceptor

outer segments. The disease is characterized by choriocapillaris Atrophy and by accumulation of lipofuscin, an age-related pigment, in RPE, Leading to PR degeneration. Patients affected by STGD1 usually Experience a rapid bilateral central visual loss with dyschomatopsia and central Scotoma. Disease-causing variants of ABCA4 are also associated with cone, rod, And rod-cone dystrophies.STGD1 is the most common cause of macular degeneration In children and young adults, with a prevalence of 1 in 8,000 to 1 in 10,000 people. STGD1 is an autosomal Recessive disease caused by a mutation in the ATP-binding Cassette subfamily A member 4 (ABCA4) gene. The ABCA4 protein is a transporter localized to rod and cone Outer segment discs where it facilitates the transport of Retinoids from the photoreceptors to the RPE cells. Mutations in ABCA4 results in the accumulation of toxic Material within the RPE layer and decreased kinetics of the Retinoid cycle. Subsequent degeneration of the RPE Leads to the dysfunction and degeneration of the overlying Photoreceptor layer. Similar to AMD, patients with STGD1 present with progressive central vision loss. Albeit at a much younger age of onset. The hallmark clinical Features of STGD1 are yellow pisiform flecks at the level of The RPE in the macula Gene therapy is being explored as therapy for STGD1. One issue that makes this disease challenging to address Through gene therapy is the relatively large size of The ABCA4 gene that exceeds the carrying capacity of Conventional adeno-associated virus (AAV) vectors. The AAV carrying capacity is considered to be limited to 4.7 kB. However, this size limitation appears not to be Absolute. AAV serotype-dependent packaging of much Larger cargo (up to approximately 8.9 kB of genome) has Been shown to be effective for gene delivery in mouse Models. Dual AAV vectors have been studied as a way To produce large gene reconstitution by trans-splicing and/ Or homologous recombination. Lentiviral vectors, with A substantially larger carrying capacity than AAV, have also Been used to deliver the ABCA4 gene therapeutically. Additional gene delivery techniques, including helper Dependent adenoviral particles and nonviral DNA particles, May also support the delivery of large DNA material. Since gene therapy is not likely to replace the Photoreceptors and RPE cells lost in advanced stages of this Condition, this condition is also a target for PSC therapy.

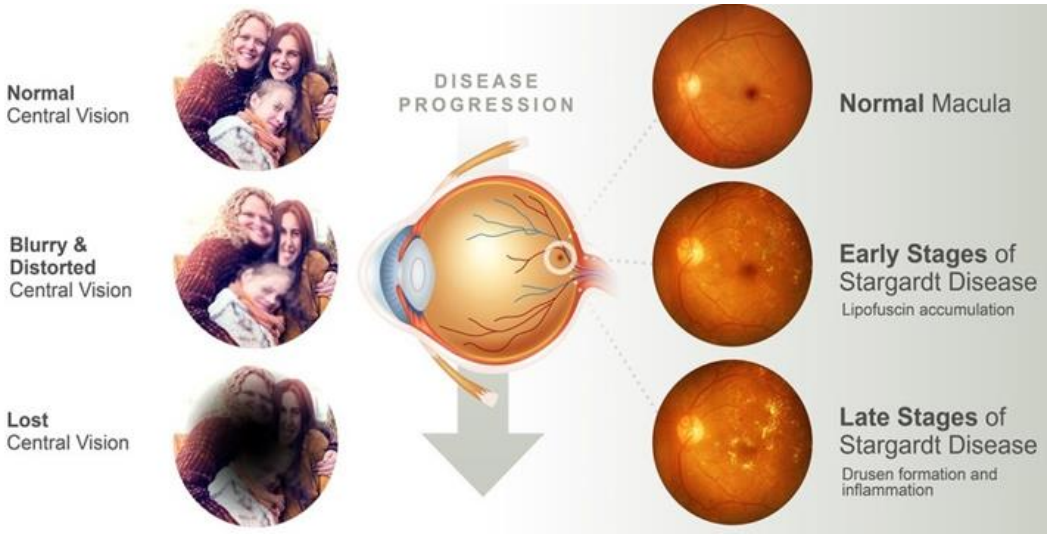

Fig.3) Disease Affected Eyes and Vision of Patient

4. Diabetic Retinopathy

Diabetic retinopathy (DR) is a vascular complication that occurs in diabetic patients. DR pathogenesis is associated with inflammation processes leading to microcirculation Damage. As a result, a disruption of the blood-retina barrier (BRB) develops, mainly Due to pericyte loss, which represents one of the earliest hallmarks of DR. To Date, only limited beneficial effects have been obtained with available therapeutic Strategies. In fact, pericyte loss is virtually irreversible since in the adult retina they are Not able to replicate. Medical options trying to mitigate DR-induced damage Include laser surgery, vitrectomy, and pharmacotherapy. However, these treatments Are generally carried out when the disease is already in an advanced state. In addition, DR also affects retinal neuronal and glial cells. In fact, the visual loss occurring in the Early stages of DR is related to retinal sensory dysfunction, mainly due to RGC loss.For these reasons, many studies are focusing on developing therapies that can mitigate Or arrest disease progression before irreversible damage occur.

Cell-Based Therapy

One approach for vision restoration in AMD, RP, or STGD1 is cell-based Therapy, which has two objectives: (1) to replace dysfunctional cells with new Retinal cells derived from stem cells that could integrate the host tissue and Restore retina function, and (2) to release trophic factors that contribute to Rescue effect. To be functional, transplanted cells must integrate, Demonstrate long-term survival and form new synaptic connections with the Host retina. Moreover, the secretion of neurotrophic factors by grafted cells Can protect the retina from degeneration and contribute to vision restoration. For example, the brain-derived neurotrophic factor is expressed in Müller cells And retinal ganglion cells and is essential for the development of neurons, Cell survival, and synaptic activity. Mainly expressed in RPE end PR, ciliary neurotrophic factor and glial cell-derived neurotrophic Factor also have neuroprotective effects. Ciliary neurotrophic factor enhances The survival of PR and promotes the axonal regeneration of retinal ganglion Cells. Glial cell-derived neurotrophic factor mediates retinal Neuroprotection through Müller cell activation involved in PR survival, retinal Structural stabilization, and inflammatory modulation. Moreover, it has been shown that intravitreal injection of Ciliary neurotrophic factor inhibits the progression of retinal degeneration and Preserves the retina function in animal models of retinal degeneration. Based on these neuroprotective effects, ciliary neurotrophic Factor-based therapy has been tested in several clinical trials, but therapeutic Effects are not sufficient for AMD or RP .In cases of cell transplantation aimed at releasing trophic factors, different Types of cells have been tested in clinical trials: bone marrow-derived Mesenchymal stem cells (BMSCs), human umbilical tissue-derived cells (hUTCs), and retinal progenitor cells (RPCs). For replacement of dysfunctional cells, candidate cells are PRs, RPEs, Müller glial cells, and retinal ganglion cell-derived from human embryonic Stem cells (hESCs)/human induced pluripotent stem cells (hiPSCs), even if at Present ohESC/hiPSC-RPE cells are used in clinical trials.

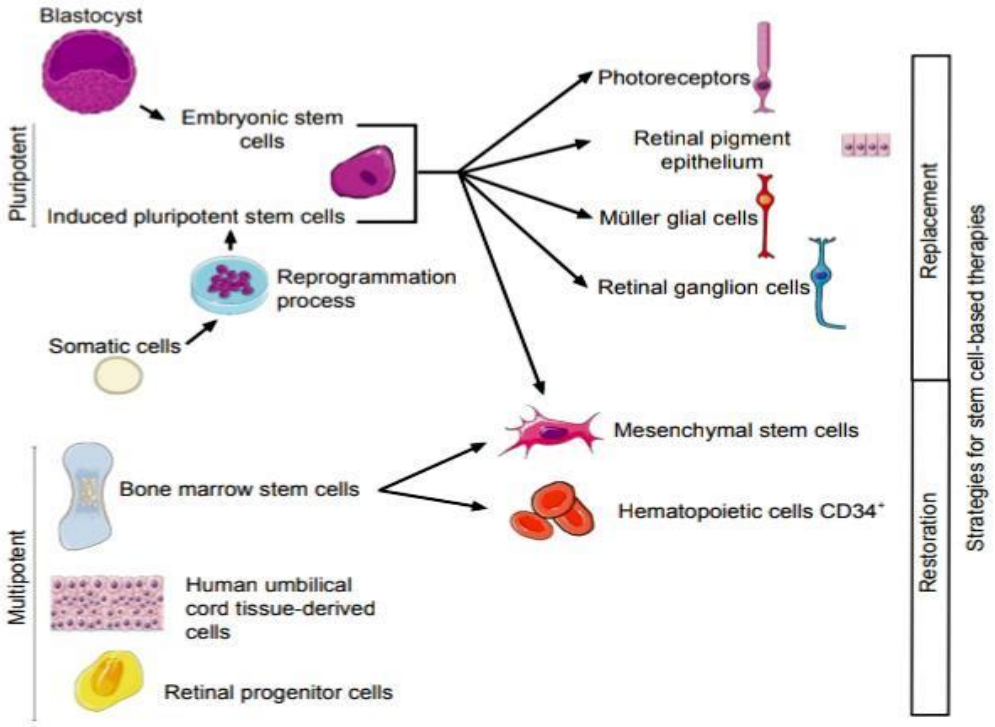

Fig.4) Two strategies for stem cell-based therapies: replacement or restoration Of dysfunctional cells.

Cell Source

Stem cells have the ability to differentiate into other cell types from all three Germ layers: ectoderm, mesoderm, and endoderm. Thanks to their potential, Much research has been done to use stem cells to replace or repair damaged Cells in many diseases

1) Embryonic and pluripotent stem cells

Embryonic stem cells (ESCs) are pluripotent cells derived from the inner Cell mass of blastocysts. Since their derivation from Human blastocysts, the potential application of ESCs was greatly studied In vitro, and in vivo for cell-based therapy. One major problem associated With human ESC-derived cell transplantation is an uncontrolled immune Reaction that can lead to the rejection of grafted cells, requiring the use Of immunosuppressors. A potential alternative to avoid Immunological rejection is the use of induced pluripotent stem cells (iPSCs), Which could be derived from patient-specific somatic cells. The first derivation of hiPSC occurred in 2007. Like ESCs, iPSCs are pluripotent stem cells that can be differentiated into all Lineages of the body. They are similar to ESC in terms of proliferation and Differentiation capacities, and morphology. iPSCs are Obtained by reprogramming various somatic cells, such as fibroblasts, blood Cells, and urine cells, by different methods including episomal DNA plasmid, Sendai virus, adenovirus, mRNAs, and proteins. At the beginning, the reprogramming method consisted in introduction into Somatic cells of four transcription factors (c-Myc, Oct4, Sox2, and Flf4) by Retroviral vectors. The use of c-Myc, a pro-oncogene, And retroviral vectors, which can cause genomic mutation, made this method Inapplicable in human clinical trials. Several studies Have raised concerns over the genetic and epigenetic abnormalities of iPSC Induced by the reprogramming process. At present, many protocols exist to Obtain suitable

iPSCs for clinical trials from somatic cells, with L-Myc instead Of c-Myc, in non-integrative methods for reprogramming. The generation of iPSCs from somatic cells enables us to obtain stem cells Without using human embryos, which raises ethical issues. Cells for transplantation derived from iPSCs could overcome Ethical concerns. In fact, the isolation and use of ESCs from preimplantation Embryos produced by in vitro fertilization raise ethical issues. One approach To overcome this issue is the use of hiPSCs. One advantage of iPSC is the Possibility to obtain cells from various human leucocyte antigen (HLA) Types. HLA typing is used to match patients and donors For transplantation. In this context, the creation of HLA-iPSC obtained From donors of blood group O (compatible with all blood groups) bank is Considered as a future clinical strategy for HLA-matched cell transplantation To minimize the risk of graft rejection. However, the utilization of iPSCs for cell therapy also has some drawbacks Such as epigenetic memory. Indeed, it has been shown that RPE cell derived From hiPSC (obtained after fibroblast reprogramming) retains a "memory" Of gene expression patterns of the cell of origin. These Lineage-specific imprints in hiPSC could affect certain cell properties such as Proliferation and senescence. Moreover, due to their unlimited proliferative Capacity, many questions have been raised about serious safety issues. Indeed, It is well-established that undifferentiated cells can generate teratomas or Teratocarcinomas and induce potential immune reactions when. According to the literature, teratoma formation is Expected to begin within the first few months after. Therefore, before clinical application of pluripotent stem cell Materials, it is mandatory to develop robust differentiation protocols in Order to eliminate pluripotent cells and minimize the risk of abnormal cell Proliferation.

2) BMSCs and HUTCS

BMSCs are located in the bone marrow, which has the highest proportion of Adult stem cells. Two types of BMSCs are defined: mesenchymal stem cells (MSCs) and hematopoietic stem cells, also called CD34+ Cells. These cells are multipotent, and They have a capacity for differentiation but it is more limited than pluripotent Stem cells, and show paracrine trophic effects with secretion of neurotrophic Factors or anti-inflammatory modulators. MSCs represent less than 0.1% of The cells in bone marrow but can be expanded easily in vitro. They are also Found in many tissues such as teeth or liver. BMSCs have many advantages: they are able to migrate toward lesion sites And they have the capacity for trans-differentiation (ability to differentiate Into cells of other organs in specific environment). When RPE cells Are damaged, they express specific chemoattractive cytokines/chemokines That induce migration of BMSCs to the injured site (Park et al., 2021). Once On the site, they can transdifferentiate into retinal cells [RPE cells and PRs] to repair the damaged tissue. BMSCs can also produce neurotrophic factors to promote cell survival and Anti-inflammatory effects. Another advantage is that CD34+ Cells are easily Obtained from patients and require minimal manipulation before use during Autologous procedures for transplantation. hUTCs are derived from extra-embryonic mesoderm: cord tissue or cord blood component. The factors secreted by hUTCs include growth factors (hepatocyte growth factor, glial cell-derived neurotrophic factor, etc.),multiple receptor tyrosine kinase ligands, bridge molecules, and cytokines. These cells also secrete the thrombospondin family proteins involved in Synaptic connectivity and neuronal growth.

3) RPCs

RPCs are the cells at the origin of retina formation during embryonic Development and represent a highly interesting source of cells in retinal Therapies. They can be obtained from the retina of human fetuses between 16 and 20 weeks of gestation. They are able to migrate And differentiate along the PR lineage and may have the potential to replace Rods and cones in degenerative retinal disease. Transplantation of RPCs has Two advantages: promoting neuroprotection by secretion of trophic factors That enhance retinal survival (insulin-like growth factor-1, hemodiafiltration, Etc.), and photoreceptor replacement.

❖ ***Which type of cells for transplantation?***

- Restoration of vision using a single type of retinal cell seems simplistic and Optimistic especially in case of progressive retinal diseases. Indeed, the retina Is composed of a highly complex layered structure where more than one Type of cell is generally affected in retinal disease, due to the high degree of Cellular interconnection. For example, during AMD, progressive RPE cell death Is followed by underlying PR degeneration. Multiple studies have shown That hiPSCs/hESCs can evolve toward a three-dimensional (3D) retinal tissue With major retinal cell populations organized in different layers (Zhong et al., 2014; Hallam et al., 2018). The ability of ESCs/iPSCs to form retina in a dish is Currently being developed to investigate retinal disease progression and as a

❖ ***Tissue for cell transplantation***

Currently, clinical trials are focused on transplantation of RPE cells derived From hESCs or hiPSCs to cure retinal degeneration.Stem Cells for Retinal Diseases Stem cells were tested in several clinical trials, and the Approaches include transplantation of undifferentiated Stem cells, pre-differentiated stem cells, or stem cell-Derived factors. Several studies and trials have utilized RPE cells derived from hESCs or iPSCs, and MSCs derived from various tissue sources and tested Their retinal regenerative potential. Here, we have summarIzed and analyzed the potential of each cell type for the Treatment of retinal disorders.

Preclinical Studies with Stem Cells

1. ESCs,

due to their extensive proliferative and differentiation potential, have been used as a cell source to treat Various degenerative diseases, including retinal degeneration. Subretinal transplantation ***ESCs*** of hESC-derived RPE cells In a preclinical mouse model of AMD showed no tumor Growth with the transplanted cells detected at the injection Site seven months after injection, and some injected cells Formed an RPE monolayer above the native layer. In A similar study, RPCs derived from hESCs integrated Into the mouse ganglion cell layer (GCL), expressed retInal ganglion cells (RGCs) marker Brn3a,and outer Nuclear layer (ONL) thickness increased in the injected Animals. In a study involving non-human primates, sub Retinal transplantation of hESC-derived retinal organoids Was well tolerated and the transplanted cells integrated into the retinal layer in the injury site created by laser Ablation.

2. iPSC

iPSCs, similar to ESCs, have pluripotent differentiation ability but without ethical concerns. The human iPSC-derived retina was transplanted into the subretinal space of monkeys with laser-induced retinal injury and immune-deficient rats with RP. The transplanted cells integrated into the rat retina and formed Synaptic connections with

the host bipolar cells. In the monkey Model, the transplanted cells integrated into the host retinal Layer and improved electroretinogram (ERG) and visual Guided saccade (VGS) scores were observed. Similarly, in An RP mouse model, subretinal transplantation of iPSC-Derived RPE spheroids delayed thinning of retinal ONL, Increased pigment epithelium-derived factor (PEDF) levels, Reduced the number of apoptotic cells as well as microglial Infiltration in the retina. In Royal College of Surgeons (RCS) Rats with an inherited mutation of MER proto-oncogene tyrosine kinase (MERTK) gene as a model of retinal degeneration, subretinal transplantation of iPSC-derived RPE cells Significantly rescued visual function as measured by optokinetic tracking thresholds (OKT). None of the animals showed Abnormal proliferation or teratoma formation; however, the Graft was compromised in two animals due to inflammatory Response.15 Interestingly, co-transplantation of RPCs and RPE Cells derived from iPSCs was superior to transplanting individual cell types, it resulted in better visual response and preservation of ONL in a rat model of retinal degeneration.16 Further, in an animal model of RP, subretinally transplanted iPSC-derived CRX-expressing photoreceptor precursors engrafted at the inner nuclear layer (INL). The transplanted cells expressed the pan cone marker, Arrestin, indicating further maturation. In a preclinical study with rats and pigs, iPSCs obtained from AMD patient CD34+ cells, when differentiated into RPE cells, integrated and rescued the retinal degeneration. In this study, the authors found that, compared to suspension cells, ten times fewer RPE cells were required to achieve the same therapeutic effect when transplanted as a monolayer. Whereas RPE cells transplanted as cell suspension failed to integrate into the rat RPE layer, poly (lactic-co-glycolic acid) (PLGA) based scaffold facilitated the integration of transplanted RPE patch into the rat Bruch's membrane.18 Stem cell-based therapies have also been explored as an option To treat retinal ischemic injuries with abnormal endothelial Progenitor cells (EPCs) prevalent in diabetic patients. hiPSC-Derived endothelial cells alleviated oxygen-induced retinal injury in mouse models and reduced pathological vasoobliteration and neovascular tufts.

3. MSCs

MSCs have been studied extensively for their potential in the Treatment of several retinal disorders. Here, we have discussed Some recent reports that utilized MSCs in the preclinical modEls of retinal degeneration. Human dental-pulp-derived MSCs (DP-MSCs) on intravitreal transplantation improved the retinal Function in a rat model of retinal degeneration,20 and rat bone Marrow-derived MSCs (BM-MSCs) rescued the ONL thick-Ness by enhancing autophagy. Intravitreal injection of umbical cord-derived MSCs (UC-MSCs), and the exosomes Derived from UC-MSCs suppressed inflammatory response, Retinal damage and improved the visual functions in a mouse Model of retinal injury. Injection of mouse BM-MSCs or Paracrine factors derived from BM-MSCs into the anterior Ocular chamber induced proliferation of progenitor cells in The ciliary body and promoted ocular regeneration and repair In a glaucoma mouse model. Similarly, conditioned media (CM) from BM-MSCs containing the paracrine factors significantly reduced the intraocular pressure (IOP) and protected The host RGCs.Intravenous injection of UC-MSCs reduced Diabetes-associated microvascular leakage in the retina by Upregulating the expression of tight junction protein Occludin. In a streptozotocin-induced diabetic mouse model Of DR, intravitreal injection of adipose tissue-derived MSCs (AD-MSCs) increased intraocular levels of neurotrophic factors

and prevented the loss of RGCs. Several studies have analyzed the potential of MSC-Derived factors, cells, and engineered MSCs to repair the Damaged retina. Extracellular vesicles derived from human BM-MSCs significantly protected RGCs and prevented retinal Nerve fiber layer thinning in a preclinical rat model of Glaucoma. Injection of the stromal fraction of adipose tissue, Which is enriched with pericytes, decreased vascular leakage, Apoptosis and improved the "b" wave amplitude in a DR Mouse model. Similar reductions in vascular leakage and Improvements in visual acuity were observed when CM Derived from human AD-MSCs were intravitreally injected In Ins2Akita mouse model of DR.29 Murine BM-MSCs genetically modified to produce neurotrophin-4 preserved the retinal Bioelectrical activity in the injured retina and completely Restored the laminated organization of the outer retina in an RP animal model.Similarly, BM-MSCs genetically engineered to express C-X-C chemokine receptor type 4 or PEDF significantly reduced the retinal damage, reduced the level of pro-inflammatory cytokines, and restored the retinal Structure and function in DR disease models. Interestingly, the Administration of neural stem cells derived from UC-MSCs Significantly improved the vision and survival of RGCs in Diabetic rats.

Clinical Trials with Stem Cells

The encouraging results obtained from preclinical studies Led to several clinical trials utilizing various stem cells and Their derivatives.

1. ESCs

In an interim report on Phase I/IIa clinical trial (NCT02286089) of 12 patients with advanced dry age Related macular degeneration (AMD) and geographic atrophy (GA), Banin et al reported that hESC-derived RPE cells were Well tolerated in patients when administered along with sysTemic immunosuppression before transplantation. Transplanted cells were detected in the subretinal space during Long-term follow-up, and improvement in the RPE layers at the GA border was observed.34 Similarly, transplantation of hESC-derived RPE cells in AMD and Stargardt macular dystrophy (SMD) patients resulted in significant improvement in visual acuity without any abnormal proliferation. A recent update by Riemann et al on the fourth cohort of patients in phase I/IIa clinical trial (NCT02286089) reported visual improvements and alterations in the appearance of drusen in the treated patients. However, formation of epiretinal membranes (ERM) and retinal detachment was observed in some patients, which were successfully treated. In another clinical trial that tested the feasibility of utilizing ESC-derived RPE cells for retinal degeneration, da Cruz et al reported improved visual acuity in two patients with severe exudative AMD after subretinal transplantation. However, one of the patients experienced a reduction in photoreceptor function during the follow-up period, and the other patient had retinal detachment, which might or might not be related to the surgical procedure.

2. iPSCs

Although ESC-derived RPE cells were functional and patients Showed improvements in visual acuity, transplantation of ESC Derived cells requires local or systemic immunosuppression. With the recent utilization of iPSCs to treat several disorders, Mandai et al reported interesting outcomes in the clinical trials With transplantation of iPSC-derived RPE cells. Autologous Transplantation of iPSC-derived RPE cells in a patient with Advanced neovascular AMD was well tolerated, and although The transplanted cell layer was intact, no improvement in the visual acuity

was observed one year after the transplantation. A four-year follow-up on the same patient found that the Transplanted cells supported the photoreceptors, and the visual Acuity remained stable without anti-VEGF administration.

3. MSC's

Mesenchymal stem cells (MSCs) and their derivatives were Tested in numerous preclinical and clinical trials to treat retinal Disorders. In Phase I clinical trial on 4 Asian patients with Traumatic optic neuropathy, Sung et al found that sub-tenon Transplantation of human placenta-derived MSCs (PD-MSCs) Was safe without any adverse inflammatory or proliferative Side effects. PD-MSCs had a protective effect on RGCs, rescued the expression of Tuj1 and GFAP, which was concurrent With improved visual acuity. In a non-randomized phase I clinical trial of 14 patients with RP, autologous BM-MSCs Were transplanted intravitreally, and the improvement in visual Function was assessed between 1 and 7 years. Immediately After transplantation, an increase in IOP was observed in all the Patients that returned to baseline after 24hr. All the participants Showed improvement in BCVA (best-corrected visual acuity) A few months after transplantation; however, it returned to Baseline within 12 months, and no further deterioration of the Condition was observed. One of the participants developed A condition called osseous metaplasia in the ciliary body in The third year of follow-up, and another patient developed Intraocular lens (IOL) subluxation in the fourth year. In Phase III clinical trial, Kahraman et al transplanted UCMSCs into the suprachoroidal area of 82 RP patients involving 124 eyes. At a 6-month follow-up, 46% of eyes experienced an Improvement in the vision, 42% of eyes remained stable, and 12% of eyes had the condition worsening, but none experienced adverse events. Similarly, in a phase I/II clinical trial of 32 RP patients, when UC-MSCs were administered intravenously, 90.6% of patients had improved visual acuity at 12- Months follow-up. None of the patients experienced adverse Effects; however, the average visual field sensitivity and flash Visual evoked potential remained the same for all the patients Following the transplantation. Several other clinical trials in RP patients reported improved visual acuity or significant Changes when BM-MSCs were transplanted. In phase III Clinical trial on 32 patients involving 34 eyes with RP, sub Tenon transplantation of Wharton's jelly-derived MSCs (WJ-MSCs) significantly improved BCVA, visual field, and outer Retinal thickness during a 6-month follow-up. The transplanted Cells did not induce any adverse side-effects with the study still On-going. In a clinical trial involving patients with proliferative DR (PDR) and non-proliferative DR (NPDR), intravenous transplantation of autologous BM-MSCs significantly Improved the BCVA at 3- and 6-months follow-up period in The NPDR group but not the PDR patients. Injection of BM-MSCs was followed by intravenous administration of dexa-Methasone sodium, and the transplantation did not cause any Adverse immune reactions systemically or at the ocular site. In another clinical trial involving two patients with advanced Glaucoma, with intravitreal injection of autologous BM-MSCs, None of the patients showed improvements in visual acuity or Visual field during a 12-month follow-up, but one of the Patients experienced retinal detachment two-weeks after the Treatment initiation.48 In addition to transplantation of stem cells cultured ex vivo Before transplantation, a few clinical trials examined the direct Injection of stem cell population isolated from bone marrow or Adipose tissue. Recently, Wiącek et al reported intravitreal Transplantation of autologous bone marrow-derived lineage-Negative (BM line) cells in RP patients with the disease incidence ranging from few years to more than 10 years. A

significant improvement in the BCVA and BCDVA (best-Corrected distance visual acuity) was reported by the patients at The 12-months follow-up period, and improvement in the Visual parameters was more pronounced in patients who had Symptoms for less than 10 years and maintained functional Foveal cones. The study also reported retinal detachment in Three cases, with two cases requiring surgery to achieve complete retinal attachment. In two separate clinical trials, Limoli Et al transplanted autologous adipose-derived stem cells (ADSCs) from the stromal vascular fraction of the adipose Tissue along with platelets obtained from platelet-rich plasma And adipose stromal cells of the orbital fat in the subscleral Space. The study reported an improvement in visual performance with no adverse effects. In an experimental clinical Trial, when patients with refractory macular holes were injected With either UC-MSCs or exosomes derived from UC-MSCs, Improvement in BCVA and closure of macular holes in six out Of seven patients was observed. No adverse reaction was Observed, except one patient who showed inflammatory Response due to the high dose of exosomes.

Challenges And Limitations

Despite the potential of stem cell therapy, several challenges remain:

- **Immune Rejection:** Risk of immune response against transplanted cells.
- **Tumorigenicity:** Potential for uncontrolled cell growth and tumor formation.
- **Ethical Issues:** Concerns over the use of embryonic stem cells.
- **Differentiation Control:** Ensuring correct lineage differentiation and functional integration.

CONCLUSION

Stem cell therapy has emerged as a promising avenue for the treatment of retinal damage, offering potential solutions for currently incurable degenerative retinal diseases such as age-related macular degeneration (AMD), retinitis pigmentosa (RP), and diabetic retinopathy (DR). Various stem cell sources, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and retinal progenitor cells (RPCs), have shown encouraging results in preclinical and early-phase clinical trials. These cells exhibit the capacity to differentiate into retinal cell types, integrate into damaged retinal tissue, and provide neuroprotection through paracrine effects. Despite these promising advancements, several challenges remain before stem cell therapy can be widely implemented in clinical practice. Issues such as immune rejection, tumorigenicity, ethical concerns, and the risk of uncontrolled differentiation must be addressed. Additionally, optimizing transplantation techniques, improving graft survival, and ensuring long-term functional integration into the retina are critical areas requiring further research. Future studies should focus on refining differentiation protocols, developing safer gene-editing techniques, and utilizing bioengineering approaches to enhance cell delivery and survival. Large-scale, well-designed clinical trials are essential to establish the safety, efficacy, and long-term benefits of stem cell therapy for retinal diseases. With continued advancements in regenerative medicine and biotechnology, stem cell-based therapies hold great promise for restoring vision and improving the quality of life for patients with retinal damage.

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