

Cell Therapy: An Emerging Treatment Strategy of the Current Era for ophthalmic diseases



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Cell therapy has emerged as a hope for incurable diseases, which aims to replace disordered cells with able cell populations to repair the underlying cause of disease initiation and progression. Over the past century, average human life expectancy has increased due to the advancement in medical science in the diagnosis and treatment of diseases as well as the accessibility of healthcare. However, with the increasing lifespan, age-related disorders have increased drastically. There is an unmet need to develop effective treatment strategies for age-related disorders, including neurological, autoimmune, skeletal, renal, liver, and ophthalmologic diseases. The current treatment strategy for chronic degenerative diseases only relies on palliative treatments that aim to delay the disease's progression. Organ transplantation is one of the options with limited success many times due to the immune response, rejection, shortage of available donors, and chronic immunosuppressive treatment following surgery. Therefore, regenerative medicines using various types of cells, including primary, progenitor, or stem cells, have emerged as promising treatment strategies. In recent years, stem-cell based therapies have found success in the clinical trials (1, 2). Stem cells have the limitless replicative potential, and the ability to generate all types of cells. Many cell therapies that reach advanced clinical trials are based on mesenchymal stem cells. However, pluripotent stem cell research has demonstrated great potential in regenerative medicines.

With the aim of repairing diseased organs or tissues previously thought to be irreparable, cell therapy involves the replacement of aberrantly functional or injured tissue by engrafting, stimulation of the self-healing process of existing endogenous tissues by releasing growth factors and cytokines, and use of genetically modified cells to deliver therapies. Several cell types are used for the purpose, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), adult/fetal SCs, including mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), mononuclear cells (MNCs), endothelial progenitor cells (EPCs), and neural stem cells (NSCs), and several tissue-specific primary cells. ESCs are isolated from the inner cell population of the blastocyst. ESCs have unlimited differentiation potential, which is highly beneficial for the success of cell therapy. However, the challenge lies in isolating a pure population of differentiated cells. iPSCs are of stem cell origin and programmed to exhibit pluripotency by introducing several factors. Long-term genetic stability is a challenge for this class of cells. Adult/Fetal SCs are isolated from specific tissues, including bone marrow, placenta, umbilical cord, blood, adipose, or other specialized tissues of interest.

Cell-based therapies have shown promising implementation in ophthalmic diseases (3). Cell replacement has been found to be beneficial for the treatment of retinal cell death associated with multiple ocular dysfunctions, including age-related macular degeneration (AMD), glaucoma, retinitis pigmentosa (RP), and juvenile macular degeneration or Stargardt's disease (SD). The irreversible loss of retinal cells initiates the disease. The underlying cause of the disease progression is genetic abnormalities in the retinal pigmented epithelial cells and photoreceptors. The damage in retinal pigmented epithelium (RPE) cells and photoreceptors causes central vision loss in SD. On the other hand, the degradation of retinal ganglion cells (RGCs) is found in glaucoma patients. There is no treatment to reverse the loss, and transplantation-based therapeutic approach has only shown the ray of hope. Various cell types of retina derived from pluripotent stem cells such as retinal pigmented epithelium cells, photoreceptor cells, RGCs, and retinal organoids provide cell source for transplantation.

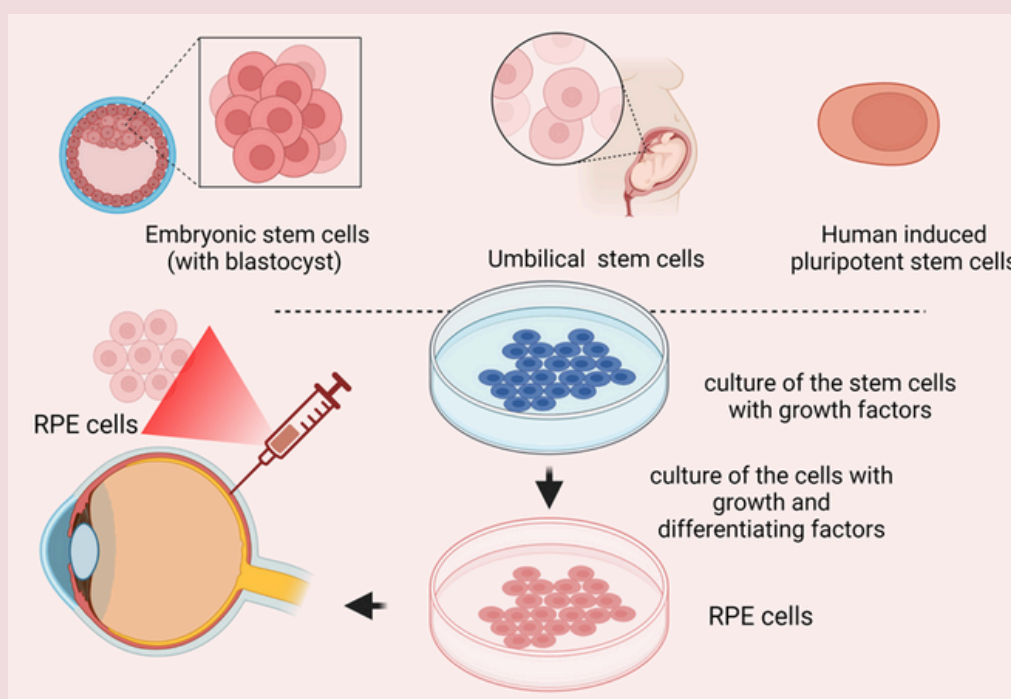


Figure 1. Stem cell-based therapy for retinal degenerative diseases.

Human embryonic stem cells (hESC) and induced pluripotent stem cells have been explored to correct ocular dysfunctions (4). The RPE replacement is evolving as a feasible approach for treating age-related macular degeneration. In several preclinical studies, RPE cells were transplanted as a cell suspension into the immunosuppressed animal eyes. The transplant effect were monitored on a short-term basis. In a study, hESC cells were directly differentiated towards RPE cells under certain cell culture conditions (5). The general protocol has been shown in Figure 1. The hESCs differentiated in presence of nicotinamide, which upregulated transforming growth factor, TGF- β , resulting in development of RPE cells during embryogenesis. The hESC-derived cells showed morphology, expression of markers, and functions of authentic RPE cells. Transcriptome analysis was used for comparative assessment of putative RPE cells obtained from hESCs and human fetal RPE (6). The hES cell derived RPE cells expressed molecular markers, could perform phagocytosis, and were able to differentiate into cells of Royal College of Surgeons (RCS) rats (7). Cultures of 67-passages established from 18 different hESCs and RPE cells derived from NIH-approved hESCs were able to rescue

Cultures of 67-passages established from 18 different hESCs and RPE cells derived from NIH-approved hESCs were able to rescue photoreceptors in animal model of retinal disease. The results were highly promising with 100 % improvement in visual performance compared to untreated controls. In a recent study, long-term transplant effect of iPSC-RPE cells grown in monolayers was assessed in immunocompromised RCE rats (8). In this study, the RPE cells of iPSC origin were cultured on a nanoengineered ultrathin parylene C scaffold, which was transplanted into the subretinal space of immunocompromised RCS rats pups and evaluated 1,4, and 11 months following transplantation. Interestingly, transplant remained as a monolayer and expressed RPE-specific markers, performed phagocytosis, and preserved the vision. The RPE survival of only 50% of the eyes were observed after 11-months post-implantation. Loss of the cellular characteristics could be due to the immune reactions via macrophage activation, fibrosis in peri-membrane, and transition of cell's fate towards mesenchyme (as judged by the upregulation of mesenchymal markers). Mesenchymal stem cells exhibit benefits towards neuroprotection, however, their sub-optimal capacity to differentiate in the in vivo condition reduces their therapeutic activity (9). A study reported direct conversion of human umbilical cord mesenchymal stem cells into RPE cells for the treatment of retinal degeneration (9). A cocktail of 5 transcription factors, including CRX, C-MYC, NR2E1, LHX2, and SIX6 were used to differentiate the stem cells to RPE cells. The cells demonstrated epithelial-to-mesenchymal transition (EMT)-inhibitory ability. Moreover, grafting of the cells in the subretinal space in rat induced with AMD demonstrated reversal of AMD pathophysiology.

There is a recent report of a phase I clinical study, where an RPE patch consisting of a fully differentiated RPE cells grown in monolayer on a suitably coated synthetic basement membrane were administered using a microsurgical tool into the subretinal space of an eye in two patients (1). The endpoints were the sign of adverse effects and the proportion of subjects with improved visual acuity of 15 letters or more. Visual acuity was found to be 29 and 21 letters in two subjects, respectively over 12 months. The patients received immunosuppressive drugs during the 12 months to avoid implant-related immune reactions. Long-term safety of the transplantation of human retinal progenitor cells were evaluated in retinitis pigmentosa patients (10). The RPE cells transplantation in retinitis pigmentosa patients did not cause tumorigenesis when immunosuppressive agents were not administered. Moreover, a significant improvement in visual acuity ($P < 0.05$) were registered in patients.

The stem cell therapy shows efficacy in the in vivo systems and clinical trials, however, it is challenging and requires investigation to determine the optimal stage for cryopreservation of the hESC-derived RPE cells. A recent study published in 2022 proposed that the differentiated RPE cells could be frozen during their exponential phase, which resulted in a best post-thawing outcome in terms of cell viability and RPE cell properties and functions (11). While cryopreservation of the cells in optimal condition is important for the cells viability and performance, the delivery protocol is also another concern in the whole therapeutic regimen. The cells would be delivered to the subretinal space through a surgical procedure through a microcatheter to be inserted through sclera using a viscoelastic material (12). The device with a lighted tip is used to guide the application inside the eye.

The delivery to the suprachoroidal space other than subretinal space is needed for precision. However, this task is challenging with the possibility of bleeding from the highly vascular choroid.

Future perspectives:

The stem cell therapy has emerged as a promising strategy to restore vision in retinal degenerative diseases. A decade ago, this idea was limited to the laboratory level. Thanks to the continuous advancement in this area of research, which paved the way for this treatment to go to the human clinical trial. There are few major concerns which needs to be addressed. The cell source is an important factor in the cell replacement therapy. The quality, type, and the viability of the cells are concerns. Even though, so far, in the completed clinical trials, there was no tumorigenicity of the implanted cells. However, tumorigenicity of the stem cells are a great concern. RPE cells survive better as a sheet form than as a cell suspension. However, it is challenging to maintain a sheet form during transplant surgery, needing skilled surgical intervention. There is a huge immunological concern which cannot ignored. Stem cell research has given a ray of hope for ocular degenerative diseases, and successfully translated to human clinical trials. Therefore, beyond all doubts, the effort of the research community would fully harness the power of stem cell therapy in neuro-retinal regeneration in near future.

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