Review Article

Ocular Disorders and Stem Cell Therapy: A Review

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Abstract

Sustenance of visual function is the ultimate focus of ophthalmologists. Failure of complete recovery of visual function and complications that follow conventional treatments have shifted search to a new form of therapy using stem cells. Stem cell progenitors play a major role in replenishing degenerated cells despite being present in low quantity and quiescence in our body. Unlike other tissues and cells, regeneration of new optic cells responsible for visual function is rarely observed. Understanding the transcription factors and genes responsible for optic cells development will assist scientists in formulating a strategy to activate and direct stem cells renewal and differentiation. We review the processes of human eye development and address the strategies that have been exploited in an effort to regain visual function in the preclinical and clinical state. The update of clinical findings of patients receiving stem cell treatment is also presented.

Keywords: Optic cells, stem cell, vision

Introduction

Blindness or loss of visual function can be caused by failure of the light path to reach the retina or failure of the retina to capture and convert light to an electrochemical signal before transmission to the brain via optic nerve. The major causes contributing to blindness include age-related macular degeneration (ARMD), diabetic retinopathy, cataracts, and glaucoma, which are genetically linked and associated with multiple risk factors including diet, hypertension, pregnancy, and smoking. The occurrences of these pathologies increase with the age of the patient and are thus widely spread among aging populations. Blindness is an extensive disease that not only affects the quality of life of the patients themselves but may have a negative impact on the socioeconomic status of their immediate families.[1,2]

Treatments have aimed at protecting vision and preventing visual impairment by early diagnosis using various methods of intervention such as surgery, ionizing radiation, laser, or drug treatments. Despite the efficiencies of these treatment modalities, they do not provide a complete solution to stop the progression to blindness.[3,4]

Many findings from preclinical data have supported the notion that stem cells have the capacity to revive degenerated cells or replace cells in many major diseases including ocular disorders. Stem cells are present in all tissues in our body and are self-renewable and capable of maintaining a certain level of differentiation in response to injury for tissue repair.[5] We mainly aimed this review at both clinicians and academicians, so we presented the localization of stem cell progenitors with eye development in different regions in the eye, the functions of these progenitors, and the current clinical trials and their exploitation of non-tissue specific stem cells as alternative sources for regaining lost vision.

What Are Stem Cells?

Every organ and tissue in our bodies is made up of specialized cells that originally come from a pool of stem cells in the very early embryo. Throughout our lives, we rely to a much more limited degree on rare deposits of stem cells in certain areas of the body to regenerate organs and tissues that are injured or lost, such as our skin, our hair, our blood, and the lining of our gut. Stem

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cells are like a blank microchip that can be programmed to perform particular tasks. Under proper conditions, these cells develop or differentiate into specialized cells that carry out a specific function, such as in the skin, muscle, liver, or in the eye. Additionally, they can grow extensively without differentiating, giving rise to more stem cells. These two characteristics of pluripotency and self-renewal distinguish them from other cells in the body and give them their tremendous therapeutic promise for a wide range of degenerative diseases.[6]

The four most commonly used and described classes of stem cells are embryonic stem cells, induced pluripotent stem cells, adult stem cells, and human parthenogenetic stem cells.[7]

Use of Stem Cells for Ocular Disorders

Retinal degeneration

Retinal degeneration is a medical condition that affects the health and welfare of adults and children in the developed world. It represents a group of blinding diseases that include age-related macular disease, glaucoma, optic neuropathies, and retinal vascular complication. Many clinical trials were performed to develop treatments for these diseases. However, it was reported that those approaches were still unable to entirely cure the disease. Interestingly, a stem cell-based treatment shows an extraordinary potential to rectify some of these diseases. In the past few years, studies strongly propose that stem-cell-based therapy has the ability to correct defective function of retina photoreceptors, ganglion cells, retinal pigment epithelium (RPE), and optic nerve.[8]

Retinal pigment epithelial cells and age-related macular disease

The macula enables people to read, process faces, and drive. Degeneration of the RPE leads to malformation at the macular area of the central vision at the initial phase and eventually progressive loss of central vision. This medical condition, known as ARMD, contributes to the highest cases of blindness in the elderly population globally. ARMD could be present either in wet or in dry forms (wet and dry ARMD). Wet ARMD manifests as neovascularization, which can be successfully managed with monthly inoculation of anti-angiogenic drugs such as Lucentis.[9]

Although effective in treating wet ARMD, the monthly injection into the eye causes discomfort and inconvenience to the patient and is expensive. In contrast, dry ARMD presents as drusenoid aggregates under the basal side of the RPE layer at the early phase. These aggregations will lead to geographic atrophy with pronounced loss of the RPE and photoreceptors at later stage. Most of the ARMD cases (80 to 90% patients) occurred due to the dry form as no effective treatments have been found to date.[9,10]

Clinical trials using RPE-derived human from ESCs and other stem cell-derived therapy are ongoing and becoming a promising approach for the treatment of ARMD. Several companies and institutions are actively involved in stem cell research to treat various ocular diseases, including institutions in Japan, USA, Europe, South America, China, Iran, Taiwan, and South Korea. Stem cell therapies have been administered to over 200 patients globally. Schwartz and his colleagues performed clinical trials on patients affected by dry ARMD and Stargardt's macular dystrophy.[11] In these trials, the researchers injected 50,000 to 200,000 hESC-derived retinal pigment epithelial cells into the worst-affected retina of the patients. There were increases in the area size and sub-retinal pigmentation of patches of transplanted cells in 72% of the treated patients with dry ARMD and Stargardt's macular dystrophy at 3–15 months later. Meanwhile, in a patient with Stargardt's macular dystrophy, patches of pigmented cells were found around the boundary of baseline atrophy in RPE layer and appeared more prominent after 12 months of transplantation. Six months later, after transplantation, the superior half of the atrophic lesion was totally filled in by the transplanted retinal pigment epithelial cells. The filled area became larger in size and more pigmented sites were seen after 15 months of transplantation. It is important to emphasize that the vision-related quality of life was enhanced in both patients of atrophic ARMD and Stargardt's macular dystrophy. None of the patients have reported signs of abnormal tissue formation at either the local or ectopic site of injections or immune rejections even four months after injection.[11]

Glaucoma

Glaucoma is the most common neurodegenerative disease in the inner part of retina. Prevalence models predict an increase of glaucoma incidence to 79.6 million by 2020 worldwide, a jump from 60.5 million in 2010.[12] Similar to other neurodegenerative disorders, the loss of the nerve cell population from the central nervous system can be used to predict the risk of glaucoma. Additionally, signs of glutamate toxicity, oxidative stress, impaired axonal transport, and reactive glial changes are also well-characterized in glaucoma. However, in glaucoma, retinal ganglion cells (RGCs) predominantly die, which leads to the degeneration of the optic nerve and disconnecting the communication of signals from the retina to the brain.[13,14]

Increases in age and raised intraocular pressure can lead to the occurrence of glaucoma. Diagnosis and prescription of a suitable treatment for glaucoma can be too late as patients may present asymptomatically until the end stage of the disease, which results in significant loss of visual function. Clinically verified treatments such as medication and eye surgery could delay the development of the glaucoma by reducing intraocular pressure but fail to halt the disease entirely to prevent loss of vision. As of the date

of this review, two registered clinical trials are recruiting patients for glaucoma treatment with bone marrow-derived mesenchymal stem cells. The safety of autologous stem cells derived from adipose tissue is also currently being tested in a phase I/II clinical trial for glaucomatous neuro-degeneration.[15-17]

Optic nerve disease

The optic nerve can lead to various pathologies due to intraorbital, intracranial, intrinsic, or systemic disorders. Optic nerve diseases could also lead to life- and vision-threatening conditions. Neural loss from the optic nerve is a frequently occurring, irreversible blinding pathology that involves optic light-sensing tissue. Similar to the brain, the eye, which is a part of the central nervous system, will not be able to restore neuron loss after the occurrence of disease. The patterns of optic nerve diseases provide information to the researcher to help understand the fundamental pathological activity and establish a method to enhance advanced detection and treatment strategies. Dr. Jamadar worked in a clinical trial at Chaitanya Hospital, Pune, to evaluate the safety and efficacy of using bone marrow-derived autologous cells for treating optic nerve disease. It is hoped that the primary outcome of reducing degeneration of the optic nerve will also lead to improvement in visual function and decreased intracranial hypertension. Neurotech Pharmaceuticals also used similar RPE cell implants to administer ciliary neurotrophic factor to patients with optic nerve stroke in a separate phase I clinical trial.[15,18]

Other retinal diseases

Retinal diseases other than the major ocular diseases discussed above also cause problems. These diseases include retinal detachment and retinal vascular complications. Retinal detachment is a medical condition in which the retina separates from the back of the eye. In a case report by Wilkes *et al.*,[19] one in 10,000 people faces this problem per year. As the detachment period increases, the visual recovery reduces at an exponential rate after macula-off retinal detachment.[19] With modern surgical techniques, such as scleral buckling, pneumatic retinopexy, and pars plana vitrectomy, we can anticipate more than a 90% success rate for anatomical repair. Although these treatments show positive results anatomically, the visual result still remains displeasing due to the enduring functional injury to the macula.[20]

Clinical trials for treating retinal detachment began in the 1980s. A report by Brinton states that of 106 cases of eye trauma, 55 eyes (52%) attained final visual acuity of 20/100 after surgery. The researchers also found that patients who engaged in later vitrectomy did not achieve a better final visual outcome than those who engaged in early vitrectomy within 14 days of impairment. In a separate study, Burton found that 53% of patients who experienced macula off retinal detachments and underwent early surgery reached visual acuity of 20/20 to 20/50.[21] However, patients with long-standing detachments were not able to reap functional benefits after surgery. A case reported by Suzuki and Hirose in 1997 states that after 3 months of total retinal detachment, vision was recovered in a patient with no light perception (NLP). After undergoing two surgeries, the patient recovered counting fingers vision. The scientists hypothesized that some retinal receptors were capable of eluding the failure. Although all of these trials showed a positive result in patient visual function recovery, the treatment is applicable to only early-stage impairment and is costly and inconvenient. The use of stem cell-based therapy in retinal detachment cases might be one of the alternative treatments for early- or late-stage retinal detachment.[22]

Conclusion

Stem cell-based therapy holds an extraordinary prospective in improving the lives of people who suffer from visual disorders. Research in this area will continue to grow to develop new remedies in treating and preventing the problem of vision loss. Interestingly, stem cell-based therapy is not a one-stop general remedy; however, it carries a promising future in producing new biological elements used to treat vision loss.

Ethical consideration

Not applicable.

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Conflicts of interest

There are no conflicts of interest.

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