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Review

Stem Cell Treatment in Retinal Diseases: Recent Developments

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Abstract

Stem cells are undifferentiated cells which have the ability to self-renew and differentiate into mature cells. They are highly proliferative, implying that an unlimited number of mature cells can be generated from a given stem cell source. On this basis, stem cell replacement therapy has been evaluated in recent years as an alternative for various pathologies. Degenerative retinal diseases cause progressive visual decline which originates from continuing loss of photoreceptor cells and outer nuclear layers. Theoretically, this therapy will enable the generation of new retinal cells from stem cells to replace the damaged cells in the diseased retina. In addition, stem cells are able to perform multiple functions, such as immunoregulation, anti-apoptosis of neurons, and neurotrophin secretion. With recent progress in experimental stem cell applications, phase I/II clinical trials have been approved. These latest stem cell transplantation studies showed that this therapy is a promising approach to restore visual function in eyes with degenerative retinal diseases such as retinitis pigmentosa, Stargardts' macular dystrophy, and age-related macular degeneration. This review focuses on new developments in stem cell therapy for degenerative retinal diseases.

Keywords: Stem cell, retinal diseases, recent developments

Introduction

Degenerative retinal diseases are among the main causes of irreversible vision loss. In recent years, stem cell transplant studies aiming to restore visual function in these diseases have gained momentum. In this review, we discuss general information about stem cells and evaluate the results of recent experimental and clinical studies concerning the treatment of retinal diseases.

What is a Stem Cell

Stem cells are functionally undifferentiated, immature cells with a complex structure. These cells are capable of differentiating into other cell types of the body. When stem cells are introduced into an area, they can settle in a suitable environment where they proliferate and either propagate their own population or differentiate into various types of cells and generate cell populations of that type. They also have the potential to repair tissue and restore function after injury. Because of this potential, it is believed that they may be able to either replace or repair damaged cells in the retina. Their unique properties have led to the investigation of stem cells as a treatment option for many diseases.[1,2,3,4]

Properties of Stem Cells

Proliferation: Stem cells are able to divide and multiply for extended periods of time.

Self-renewal: After division, the resulting cell can continue as a stem cell, like the parent stem cell.

Differentiation: Stem cells are unspecialized and can give rise to specialized cells. Both internal and external stimuli are important in this process. Internal stimuli are controlled by the cell's genetic material. External stimuli are regulated by chemical factors secreted by other cells in the environment, by physical contact with neighboring cells, and by other molecules in the environment.[1,2,3,4]

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History of Stem Cells ESCs

Embryonic stem cells (ESCs) were first obtained from a mouse embryo in 1981. ESCs were first obtained from a human embryo in 1998 under laboratory conditions. In 2006, adult stem cells were reprogrammed to behave like ESCs, giving rise to "induced pluripotent stem cells" (IPSCs). The first Food and Drug Administration (FDA)-approved human trial was initiated in 2009 and used human ESCs for spinal cord injury. Stem cell research for retinal diseases started in 2010.[3,4]

Stem Cell Types and Procurement

1. ESCs

ESCs are produced in vitro from the inner cell mass of an embryo (blastocyst) removed in the first 3-5 days of early embryonic development. These cells are pluripotent because they have the ability to differentiate into any cell of the body derived from the ectoderm, mesoderm, and endoderm. It is also possible to remove these cells without destroying the embryo.[1,6]

2. Adult Stem Cells

- Mesenchymal Stem Cells (MSCs): These are found in many adult tissues, such as the blood, blood vessels, skeletal muscles, skin, teeth, bone marrow, fat, and cartilage, and are isolated from these tissues in vitro. MSCs derived from fat and bone marrow are most commonly used. These cells are considered multipotent because they can differentiate into many types of specialized cells in the body.

- IPSCs: These are derived by conferring ESC properties to cells obtained from adults through in vitro genetic reprogramming. Like ESCs, they are pluripotent.[7]

3. Cord Blood Stem Cells

These are isolated in vitro from cells obtained from cord blood following delivery.[1]

4. Amniotic Fluid Stem Cells

These are isolated in vitro from cells obtained from amniotic fluid.[1]

Mechanisms of Action

1. Cell replacement: Healthy stem cells can replace unhealthy or lost stem cells.[1,5,8]

2. Nutritional support: Healthy stem cells increase support to surrounding cells by secreting growth factors.[1,5,8]

3. Anti-apoptosis: Stem cells can regulate the degeneration of retinal cells and vessels by inhibiting apoptosis.[1,5,8]

4. Synapse formation: They can create new synaptic connections.[1,2,3,4,5,8]

Stem Cell Studies For Retinal Diseases

There are numerous advantages of stem cell therapy in the eye. The amount of stem cells required is low, which is important in terms of cost. The surgical approach is quite easy, and the transplanted cells can be easily monitored with the imaging methods currently used in clinical practice. The fellow eye can be used as a control. Furthermore, long-term immunosuppressive treatment is not required due to the immune privilege of the eye.[9]

In experimental studies, the application of healthy stem cells in the place of degenerated retinal cells has promoted cell regeneration, creation of new intercellular connections, and improvement of visual function. Stem cells have the potential to differentiate into many cells in their environment, including the retinal neural cells and photoreceptors. Earlier experimental studies have shown that stem cells are very compatible with retinas and are able to adapt to Müller, amacrine, bipolar, horizontal, and glial cells, and photoreceptors.[8,9]

ESCs, IPSCs, and MSCs (of bone marrow and adipose tissue origin) are used in stem cell therapy for retinal diseases.[1,2,3,4,5,8,9]

Studies on the Use of ESCs

ESCs obtained from mouse embryos were shown to be capable of expressing neural markers when induced by retinoic acid. These cells were able to migrate into the retina when applied intravitreally, and although their differentiation to photoreceptors was limited, they enhanced photoreceptor viability in a retinal degeneration model.[10,11] Similarly, in another study where ESC-derived neural cells were applied subretinally and intravitreally in rats, the cells showed good retinal integration and a neuroprotective effect despite limited differentiation into photoreceptors.[12]

The results obtained with ESC-derived RPE cell transplantation are quite successful. Improvements in photoreceptor function and increased visual performance were observed in studies using a rat MERTK-defective retinal degeneration model.[13,14,15] Lu et al.[16] observed improvement in computerized assessments of visual function and visual field after the use of human ESC-derived RPE cells in rats, and showed with post-enucleation histological examinations that the cells survived for 200 days.

Following promising results from experimental studies, the US FDA approved the launch of phase I/II stem cell clinical trials for retinal diseases in humans in 2010. Human ESC-derived RPE (MA09-hRPE) cells were used in this study, which was conducted in centers across Europe and America and was supported by Advanced Cell Technology (now called Ocata Therapeutics). Schwartz et al.[17] published the first results of this study in 2012. In the preliminary report, no signs of negative proliferation, tumor formation, ectopic tissue development, or rejection were observed in 4 months of follow-up after subretinal application in one patient with Stargardt macular dystrophy and one patient with dry-type age-related macular degeneration (AMD).

Later, the 22-month follow-up results of 9 AMD patients and 9 Stargardt macular dystrophy patients were presented. Best corrected visual acuity (BCVA) increased in 10 cases while it remained stable in 7 cases and deteriorated by more than 10

letters in 1 case. There was no improvement in the patients' untreated fellow eyes. Vision-related quality of life scoring at the end of one year increased by 25 points in cases of AMD and by 20 points in cases of Stargardt macular dystrophy. This is the first study to report the medium/long-term results of stem cell application in degenerative retinal diseases.[18]

Another recent report publishes the findings of a clinical trial in which ESC-derived RPE cells (MA09-hRPE) were applied to the subretinal space in a total of four cases, two with dry AMD and two with Stargardt macular dystrophy. No adverse side effects were observed in one year of follow-up. In terms of safety, there were no adverse outcomes such as uncontrolled proliferation, tumor formation, and ectopic tissue development during the 1-year follow-up period. Visual acuity improved by 9-19 letters in 3 of the patients and remained stable in the other. These findings support the safety of ESC-derived RPE cells.[19]

These initial human studies have opened the door for further research and encouraged the inclusion of patients with better visual acuity in future trials.

Advances in stem cell therapy will continue in future studies using different RPE transplant methods in different retinal disease groups.[20]

Studies on the Use of IPSCs

The reprogramming of adult somatic fibroblast cells into IPSCs possessing ESC-like properties is accomplished in vitro by directly transferring cell nuclei or using retroviruses or lentiviruses to express transcription factors.[21,22,23]

Although IPSCs are also pluripotent like ESCs, they differ from ESCs in some respects. Because IPSCs are autologous, there is less risk of rejection and therefore, less need for immunosuppression. However, some IPSCs may trigger the T cell-mediated immune response due to their abnormal genetic composition.[24] Furthermore, the many passages made during the production of both IPSCs and ESCs gives rise to certain risks. Stimulation of X-linked oncogenes, suppression of tumor suppressor genes, and the high in vitro growth rate all increase the risk of tumor formation.[25,26] Tumor formation is believed to result from incompletely differentiated IPSCs. It is reported in preclinical models that if tumor growth occurs, it does so within the first 3-6 months.[27,28]

Studies using IPSCs in rats have reported improvement in retinal functions assessed with electroretinogram (ERG).[29,30] In an experimental study, Li et al.[31] found that human IPSCs could differentiate into RPE cells and increase retinal functions in rats. The IPSC-derived RPE cells expressed RPE cell markers, the rats showed improved ERG responses compared to the control group. This demonstrated that the cells were both morphologically and functionally RPE-like and safe. No tumors developed in any of the 34 rats used in the experiment.[31]

Human clinical trials were planned after obtaining encouraging results in experimental studies. A study was initiated in Japan investigating autologous use of IPSCs derived from a patient's epithelial cells.[32] Epithelial cells collected from the patient were transformed into RPE cells in vitro and transplanted subretinally to the same patient. This procedure was conducted on only one patient. The study was discontinued in March 2015 before repeating the procedure with a second patient. Two reasons were stated for this: 1) The regenerative medicine laws that were newly introduced in Japan prevented the continuation of the study, and 2) a genetic mutation which was not present in the original cells was detected in the IPSCs of the second patient. This was believed to be a result of mutations occurring during the induction and reprogramming process.[33]

Studies on the Use of MSCs

MSCs have a high proliferative capacity and can differentiate into cells of mesodermal, ectodermal, and endodermal origin. MSCs can be obtained from many tissues such as cord blood, peripheral blood, teeth, the central nervous system, liver, and especially bone marrow and adipose tissue. Adipose tissue is easily obtained under local anesthesia and the number of MSCs in this tissue is quite high. The acquired cells can be easily expanded in culture medium and maintain their stemness properties even after many passages. These features make adipose tissue a desirable source of stem cells.[34,35,36]

Many studies have shown that MSCs can differentiate into neuron-like cells. In addition, MSCs can repair damaged cells through their paracrine action. These cells secrete growth factors such as neurotrophic factors, repair synaptic connections, and promote the formation of functional connections.[37,38] In an experimental ocular hypertension rat model, MSCs were found to have a neuroprotective effect after intravitreal application.[39] Furthermore, MSCs have a strong immunosuppressive effect and inhibit the release of proinflammatory cytokines. For this reason, both allogenic and autologous transplantation are possible. In addition, they do not cause tumor formation and there is no ethical debate regarding their use.[40] Due to these advantages, MSCs were first applied experimentally, after which clinical trials were initiated for different disease groups in humans.

Subretinal application of MSCs repaired degenerating retinas in retinal degeneration models in rats.[41,42,43] An experimental study showed that rat MSCs obtained from culture activate Müller cell differentiation and exerted a paracrine effect by secreting growth factors. It was also reported in experimental studies that factors secreted from human MSCs prevent light-induced retinal damage.[43,44]

Studies have shown that MSCs can differentiate into different retinal cell types. Huang et al.[45] reported that MSCs differentiated into RPE-like cells with similar morphological features. Their study also demonstrated that they could

replace damaged cells when applied to damaged retinas. In an experimental study by Castanheira et al.[46], MSCs were injected into the vitreous chamber in a model of laser-induced retinal damage. After 8 weeks, they found that most of the MSCs had migrated to the ganglion cell layer and inner and outer nuclear layers, and that they expressed photoreceptor, bipolar cell, amacrine cell, and Müller glial cell markers.[46] In addition, based on findings that MSCs survive for 90 days in rat vitreous and for 6 months in other retinal tissues, these cells are considered a promising option for the treatment of degenerative retinal diseases.[47]

The positive results of experimental studies have encouraged the planning of clinical trials. In a prospective phase I study, a single dose of intravitreal autologous bone marrow-derived MSCs was applied to 3 patients with retinitis pigmentosa (RP) and 2 with cone-rod dystrophy, and no significant structural or functional toxicity was observed in the retinas in 10 months of follow-up. In the study, conducted by Siqueira et al.[48], four of the patients had an increase of 1 row in BCVA at 1 week after injection and this increase was preserved in follow-up. In a continuation of this study, MSCs were applied intravitreally to 20 patients who were followed for 1 year. The authors reported a statistically significant improvement in the patients' vision-related quality of life scores at 3 months, though the scores had returned to initial levels at 12 months. Therefore, the improvement seems to disappear over time.[49]

In another study by Park et al.[50], 3.4 million bone marrow-derived MSCs were injected intravitreally into 6 eyes with irreversible vision loss (retinal vascular diseases, hereditary or non-exudative AMD, RP). This treatment was well tolerated, with no intraocular inflammation or proliferation, and no decline in ERG and BCVA results after 6 months of follow-up.

No systemic side effects were observed in a reliability study of adipose-derived MSCs. Of the 14 case series, epiretinal membrane formation over the injection site extending to the macula was observed in 5 patients. Localized tractional detachment occured due to membrane development on the peripheral retina, and the patients required repeat vitrectomy. One patient developed a choroidal neovascular membrane which was treated with a single dose of anti-vascular endothelial growth factor agent.[51]

As MSC applications increase in number, so do reports of ocular complications related to this treatment. Kuriyan et al.[52] described three patients with elevated intraocular pressure, hemorrhagic retinopathy, and vitreous hemorrhage after intravitreal application of autologous adipose tissue-derived MSCs. They reported that the patients developed combined tractional and rhegmatogenous retinal detachment during follow-up and lost their vision. In another case report, autologous bone marrow-derived MSCs led to improved visual acuity in 2 of 3 patients with advanced RP; however, starting in the second week, the other patient developed preretinal and vitreal fibrous tissue, shallowing of the anterior chamber, and cyclitic membrane formation resulting in ocular hypotonia. This patient developed total tractional retinal detachment and subsequently lost their vision within 3 months.[53]

The suprachoroidal application described by Limoli et al.[54] may prevent the vitreoretinal complications reported after intravitreal and subretinal applications. No complications were observed and visual function improved in 36 eyes of 25 patients with dry AMD at 6 months after adipose-derived MSCs were applied under a deep scleral flap in the suprachoroidal area.

Conclusion

The results reported for phase I/II trials of stem cell applications are quite successful. No systemic side effects were observed in any of the studies. In addition, serious ocular side effects such as tumor formation and uncontrolled proliferation have not been observed. The reported improvements in visual function are encouraging and promising. However, it should not be forgotten that sight-threatening vitreoretinal complications can develop after intravitreal and subretinal applications. Larger studies with longer follow-up periods are needed to determine the place that this treatment will hold in the future. There are currently many studies in progress regarding the use of stem cells in different retinal diseases, and the results are highly anticipated.

Ethics

Peer-review: Externally and internally peer-reviewed.

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