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REVIEW

Stem cells in degenerative retinal diseases

Ali Devebacak, Filiz Afrashi

Departmant of Ophthalmology, Ege University Faculty of Medicine, Izmir, Turkey

Abstract

Degenerative retinal diseases are very common and can be encountered in all age groups. They are a major cause of blindness and result in significant morbidity. Treatment options are either very limited or not available. Therefore, it raises the need for regenerative treatments. Clinical studies have been conducted with different stem cell types and different application methods. Especially in retinal pigment epithelium replacement and studies utilizing neurotrophic effects of stem cells, significant evidence has been obtained in efficacy and safety. In this review, clinical trials were evaluated and case reports in the literature were investigated to collect clues about current knowledge, possible complications and issues that may cause concern.

Keywords: Age-related macular degeneration; bone marrow stem cell; embryonic stem cell; hematopoietic stem cell; induced pluripotent stem cell; mesenchymal stem cell; retina; retinal degeneration; retinitis pigmentosa; stem cell transplantation; stem cell.

The function of the retina is to receive light and converts it into a neural signal.[1] It performs this function by photoreceptor cells in the outer retinal layer. While the photoreceptor layer performs this function, its relationship with the surrounding structures, particularly the retinal pigment epithelium (RPE), is crucial.[1] It has been demonstrated by basic and clinical studies that dysfunction in the RPE results in photoreceptor cell apoptosis and consequent vision loss.[2]

Degenerative retinal diseases are important causes of blindness.[3] Retinal degeneration occurs in various forms such as age-related macular degeneration (AMD), Stargardt's macular dystrophy (SMD), and retinitis pigmentosa (RP). AMD is the fourth most common cause of blindness.[4] AMD has a multifactorial pathophysiology that results in photoreceptor degeneration in the macula.[5] SMD and RP are primarily genetic disorders of the RPE, followed by photoreceptor degeneration.[6,7] In these diseases, it is observed that the outer layers of the retina and RPE are affected, and the relationship between these two tissues is disrupted.[7] Since the inner retinal layers are not affected; it is thought possible to restore vision by RPE and photoreceptor replacement. Therefore, these diseases are the focus of regenerative treatment studies in the retina. The first animal studies on this subject are decades ago. RPE cell transplantation was performed in a retinal dystrophy rat model.[8] Substantial evidence has been reached regarding survival and function of transplanted RPE cells.

Stem cells are distinguished by their ability to regenerate themselves and differentiate into other type of cells.[9] They

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Correspondence: Ali Devebacak, M.D. Departmant of Ophthalmology, Ege University Faculty of Medicine, Izmir, Turkey
Phone: +90 232 390 49 08 **E-mail:** dralidevebacak@gmail.com
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differ from progenitor cells that can only differentiate into one cell type and have limited division ability.[10] They can be found in both adult and embryonic tissues. Differentiation abilities vary depending on which tissue they are derived from.[9] The cells obtained from the inner cell mass at the blastocyst stage of embryonic development have the potential to differentiate into all cell types in the human, so they are pluripotent. When isolated and cultured in vitro, they are capable of indefinitely division. These cells are known as human embryonic stem cells (hESCs).[11]

There are also stem cells in selected locations on adult tissues, called niches, such as muscle, liver, bone marrow, and corneal limbus.[12] They can differentiate into one type or a few types of cells, which makes them unipotent or multipotent.[13]

In addition, a pluripotent stem cell was derived from the mature cell with a method described in 2006.[14] It has been shown that mature human fibroblasts can be reprogrammed with transcription factors and gain pluripotency. These cells are known as induced pluripotent stem cells (iPSC). Studies about iPSCs are the most recent part of pluripotent stem cell studies in retina.

Retina, A Favorable Tissue for Stem Cell Studies

Stem cell research in the eye has primarily focused on the cornea.[15] However, cornea is not the only available tissue for stem cell researches in the eye. There are features that make the retina eligible in this regard. Thanks to the transparent structure of the eye, it can be evaluated directly. Thus, it is possible to follow the treatment success in vivo. It is immune-privileged with the contribution of the blood-retina barrier.[16] This feature may positively affects the survival of transplanted stem cells. In the early stages of degenerative retinal diseases, inner retinal layers are not affected yet. At the last stages, photoreceptor cell loss occurs as result of dysfunction in the RPE.[7] This suggests that a RPE replacement performed in the early stages of diseases may prevent vision loss. RPE is a single layer of uniform pigmented cells.[17] Therefore, it is relatively easy to differentiate from stem cells and produces in vitro. As a result, RPE is the focus of retinal stem cell studies. At present, it is the only retinal cell group that has reached the clinical trial stage in cell replacement studies.

In addition, the functions of stem cells other than regeneration are also targeted in studies. It has not been demonstrated that mesenchymal stem cells (MSCs) differentiate into RPE. However, preservation of retinal function has been observed after subretinal transplantation of MSCs in rat model of retinal degeneration.[18] It is thought that neurotrophic factors secreted by MSCs such as brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) may protect degenerated cells. The eye is very convenient to investigate such an effect because it is easy to deliver the treatment to the tissue. It can be performed in many ways such as intravitreal, subconjunctival, or subretinal.

Stem Cells in Preclinical Studies

Non-pluripotent Stem Cells

Transplantation studies have been carried out with stem cells obtained from other stem cell sources such as hematopoietic system, bone marrow, and umbilical cord.[12] Bone marrow stem cells consist of MSCs and hematopoietic stem cells (HSCs). MSCs can be obtained from both embryonic tissues and adult tissues. From embryonic tissues, they can be found in the umbilical cord blood and Wharton's jelly.[11] They can be obtained from adult tissues from different places such as bone marrow and adipose tissue. The mainstay of the studies of MSCs is their trophic effects rather than cell replacement. These cells exhibit immunomodulatory effects in the microenvironment and secrete trophic mediators such as BDNF and CNTF.[19] It has been demonstrated that retinal microcirculation increases after MSC injections.[19] HSCs may also be effective in degenerative retinopathies where vascular pathogenesis is important, such as DR, with their trophic effects on vascular tissue. It has been demonstrated in DR rat models that after intravitreal HSC transplantation, stem cells can be integrated into damaged tissue and vascular pathogenesis is slowed compared to the control group.[20]

hESCs

hESCs are obtained from the inner cell mass at the blastocyst stage of embryological development.[11] hESCs have self-renewal capability. Different types of adult human cells including RPE cells can be derived from hESCs.[21] Since they are obtained from embryo, it brings along ethical concerns. In addition, hESC transplants are allogeneic transplants so may cause an immunogenic reaction. Another concern with hESCs is that these cells have the unlimited ability to divide, so there is a risk of adverse proliferation. Therefore, before clinical studies with hESCs, cell lines that have been observed to not cause adverse proliferation in animal studies should be studied.

iPSCs

In 2006, a study was published for the first time describ-

ing the method of generating iPSCs. Dermal fibroblasts were transduced by viral vectors expressing four transcription factors (optical coherence tomography [OCT] 4, SOX2, Krüppel-like factor 4 [KLF4], and C-MYC).[14] It has been observed that mature fibroblasts reach pluripotency similar to hESCs. Subsequently, it has been observed that retinal cells can be derived from iPSCs. Subretinal injection of iPSCs derived retinal progenitor cells performed in rat models with retinal degeneration. Improvements in electroretinography findings and visual function-related behaviors were observed after treatment.[22]

Another good aspect of autologous iPSCs is that it eliminates ethical concerns as they are not embryo-sourced. Autologous transplantation is possible as they are derived from mature fibroblasts; however, it is quite costly and genetic diseases are expected to persist. To prevent these issues, it was planned to create human leukocyte antigen homozygous iPSCs culture banks.[23] Thus, cell lines derived from healthy donors can be produced and stored. It can be used in daily clinical applications at low cost in the future.

Clinical Trials About Stem Cells in Retina

Bone Marrow Derived Stem Cells (BM-SCs)

An early report of a clinical study conducted in 20 patients with RP in Brazil in 2012 was published.[24] It was reported that cystoid macular edema regressed on the 7th day after intravitreal autologous BM-HSCs injection in a patient with RP-associated macular edema. It was observed that this result persists for 1 month. It was considered highly promising. Later, in the statistical evaluations made in the 3rd month in the long-term results of the same study, a significant increase was found in the quality of life in the study group compared to the control group. However, it did not last long. There was no difference between the two groups in the 12 months quality of life assessment.[25] In another study in which BM-SC intravitreal injections were performed in six patients, it was reported that intraocular inflammation or hyperproliferation was not observed during the 6-month follow-up.[26] They did not report improvement in visual functions, but reported that they observed findings suggestive of incorporation of new cells in OCT.

Following the publication of these clinical studies, BM-SC injections in retinal diseases have been turned on. Apart from clinical study protocols, patient-funded practices have been performed in different centers. Subsequently, reports of worrying cases of the negative consequences of these practices were published.[27–30] These complications were retinal detachment and proliferative vitreoretinopathy following subretinal autologous BMSC injection,[28] epiretinal membrane (ERM) formation after intravitreal injection,[29] and central retinal artery occlusion after peribulbar injection.[27] After the development of ERM, vitrectomy was applied to the patient and CD34 + cells were found in the pathological evaluation of the membrane.[29,30] This suggests that stem cells may be directly responsible for membrane formation or indirectly by transforming into myofibroblasts.

These results show that more studies are needed for injection of BMSCs in the retina to be considered treatment option. Patients should be warned that BMSC injections carry various risks regardless of the injection site. Administration of these injections outside of clinical study protocols is currently not acceptable.

MSCs

The results of a clinical study which targeted the potential effects of MSCs on the microenvironment have been published. Wharton jelly derived MSCs are allogeneically isolated from a single donor. Stem cells were injected into the sub-tenon space in 34 eyes with diagnosis of RP. After 1-year of follow-up, no immunogenic reaction or adverse proliferation was observed. Best corrected visual acuity (BCVA) and multifocal electroretinogram (ERG) amplitude improved significantly.[31]

MSCs are relatively easy to obtain from adipose tissue. This method is less invasive and low budget. Autologous transplantation is also advantageous as it is possible. A study was published evaluating the results of total vitrectomy, followed by subretinal adipose tissue derived stem cell (ATSC) injection in 11 patients with diagnosis of RP.[32] Stem cells were isolated from subcutaneous adipose tissue from a single donor. Ocular complications were reported in six patients. It was reported that choroidal neovascular membrane (CNVM) developed in one patient at the injection site and ERM developed in five patients. It was stated that objective improvement could be observed in visual acuity, visual field, and ERG in one of the patients. There was minimal improvement in visual acuity in three patients. These patients stated that they began to see colors brighter subjectively. However, subretinal ATSC application has various complications. There is insufficient evidence for its effectiveness. More studies are needed to obtain reliable data.

In another clinical study on ATSCs, the efficacy and safety of suprachoroidal application were investigated.[33] In 11 eyes with dry AMD, the ATSC graft was implanted in the suprachoroidal area and the BCVA and microperimetry re-

sults were evaluated. To increase the amount of growth factor in the microenvironment, platelet-rich plasma has also been added to the autograft. It was reported that there was an increase in the mean BCVA (0.58 logMAR–0.38 logMAR) and the microperimetry test (11.44 dB–12.59 dB) compared to the control group at 6 months. They did not report macular edema, sub-retinal neovascular membrane, retinal detachment, or similar retinal complications. There is a potential risk of choroidal rupture and subsequent bleeding due to the surgical technique applied, but they also stated that they did not encounter such a complication. As a result, promising results have been achieved. It was thought that GFs secreted from suprachoroidal autograft were transmitted to RPE, photoreceptors, Müller cells and caused improvements by neurotrophic and angiogenic effects.

On the other hand, worrying case reports of ATSC injection associated complications have been published. Severe vision loss developed following intravitreal ATSC injection in three patients with AMD whose last recorded BCVA values before injection were in the range of 20/30–20/200.[34] Tractional retinal detachment, vitreous hemorrhage, retinal hemorrhages, lens dislocation, and intraocular hypertension have been reported in patients.[34] Subsequently, it was reported that bilateral retinal detachment occurred in one of the patients.[35] In another case report, a 44-year-old patient with RP was reported to have tractional retinal detachment and PVR after intravitreal autologous ATSC injection.[36] Chronic retinal detachment and neovascular glaucoma have been reported in a 42-year-old patient diagnosed with Usher syndrome following ATSC intravitreal injection.[37]

As a result, more evidence is needed of efficacy after ATSC injections. There are serious risks especially regarding intravitreal injections. Larger case series are needed to determine the optimal delivering method and effectiveness of ATSCs. During this period, it is important to inform patients in detail about the limited efficacy and complications of these injections.

hESCs

Since hESCs are pluripotent, they have been studied for replacement, unlike multipotent BMSCs and ATSCs. It has been shown that pigmented uniform cells displaying the characteristics of RPE cells can be differentiated from hESCs.[21] Results of a clinical study conducted with subretinal transplantation of hESC-derived RPE cells in 18 patients (9 AMD, 9 SMD) have been published.[38] No signs of adverse proliferation were found during the 36-month follow-up period. No systemic or ocular side effects related to the transplanted tissue were reported. No evidence was found in favor of immunological rejection. Side effects were reported to be related to surgery or immunosuppression. In 13 of the 18 patients, it was observed that subretinal pigment increased in the grafted areas. It was reported that BCVA was increased in ten eyes and this improvement was not observed in untreated eyes. There was an increase in quality of life in both SMD and AMD patients at three and 12 months. In yet another study, subretinal transplantation of hESC-derived RPE cells was performed in four Asian patients and the results were published.[39] In this study group consisting of 2 AMD and 2 SMD patients, ectopic tissue formation, adverse proliferation, and immunological rejection were not observed. At the end of 1 year follow-up, 9–19 letter BCVA increase was observed in three patients. There was no change in BCVA in one patient. With these studies, important evidence has been obtained regarding the long-term survival, safety, and even efficacy of pluripotent stem cells in the human retina.

On the other hand; following these studies, another clinical study in which hESC-RPE cells were implanted subretinally was published.[40] In this study of 12 patients with SMD, patients were followed for 12 months. At the end of the follow-up, no significant increase in visual acuity was achieved in any eye. There was no significant improvement in microperimetry. Hyperpigmentation was detected in the area compatible with the injection area of the patients. However, this hyperpigmentation has not been shown to have a positive effect on photoreceptor function. In one patient, localized thinning of the retina and a decrease in photosensitivity in the area where hyperpigmentation developed were reported and potential damage was thought to be possible.

In conclusion, when the current clinical trial results are evaluated, there is no consensus regarding the safety and efficacy of subretinal implantation of hESC-RPE cells, although they are promising.

hESC Derived RPE Monolayer

Subretinal injection of hESCs suspensions is not the only method for delivering. There are clinical studies involving the hESC derived RPE monolayer into the subretinal space. A single layer of hESC-RPE cells was formed on a synthetic basement membrane coated with human vitronectin.[41] This patch was implanted subretinally using a surgical device of their own design. In the 12-month follow-up of these two patients with AMD, an improvement of 29 and 21 letters in BCVA was reported. In another clinical study, a hESC-RPE mono-layer was created using a very thin Pa-

rylene material.[42] This patch was implanted subretinally in five patients with AMD. In 1 eye, BCVA improved by 17 letters and improvement in fixation were reported in two patients. There was no patient with a decrease in visual acuity. Findings indicating the integration between host photoreceptors and the transplanted RPE monolayer were observed in OCT.

As a result, regenerative treatment studies with hESC derived RPE patches are promising. As stronger evidence on its safety and efficacy is needed, studies in larger case series are required.

iPSCs

iPSC derived RPE is one of the newest options for regenerative retinal therapy research. Therefore, data from clinical studies are very limited. The most promising publication is the study of autologous iPSC derived RPE transplantation in a patient with exudative AMD.[43] CNVM was removed from the subretinal area and iPSC derived RPE was implanted. Results regarding the 4-year follow-up of the patient have been published. The organization of the outer nuclear layer remained stable in the patient 4 years after transplantation. Although the vascular structure-like remnants of CNVM removed from the patient were observed in fluorescein angiography, there was no exudative change. Anti-VEGF injection was not required. There was no significant change in visual acuity, no graft-related ocular complications or adverse proliferation observed.

More clinical research is needed on this subject to make conclusions about iPSC derived RPE transplantations. These results show promise in terms of survival and safety.

Conclusion

Degenerative retinal diseases are significantly common diseases that can affect different age groups. In advanced stages, they can cause serious vision loss. As with the exudative variant of age-related macular disease, treatment options are available to slow the progression of these diseases. However, the capabilities of these treatment options are limited and they are not effective in advanced stages. Therefore, it raises the need for regenerative treatments. Promising evidence has been obtained in clinical studies on RPE replacements and neurotrophic effects of stem cells. However, when the literature is reviewed, there are also case reports that may cause concern, especially those related to intravitreal stem cell injections. As of today, we are unfortunately far from being accepted as a treatment option. Thanks to the developing technology and studies focusing on this subject, more steps will be taken in this regard.

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