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STEM CELL TECHNOLOGY FOR RETINAL DISEASES

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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

Holoclar is currently the only clinically approved stem cell treatment for the eye. This treatment restores vision to patients with damaged corneas (the clear outermost part of the eye) by transplanting lab-grown limbal stem cells into areas of the eye lacking these cells Degenerative retinal diseases are among the main causes of irreversible vision loss. In nt 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.

Properties of stem cell

The two defining characteristics of a stem cell are perpetual self-renewal and the ability to differentiate into a specialized adult cell type. Stem cells differ from other kinds of cells in the body. All stem cells—regardless of their source—have three general properties: they are capable of dividing and renewing themselves for long periods; they are unspecialized; and they can give rise to specialized cell types.

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.

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.

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.

2. Nutritional support: Healthy stem cells increase support to surrounding cells by secreting growth factors.

3, Anti-apoptosis: Stem cells can regulate the degeneration of retinal cells and vessels by inhibiting apoptosis.

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.

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.

ESCs, IPSCs, and MSCs (of bone marrow and adipose tissue origin) are used in stem cell therapy for retinal diseases.

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. 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.

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. Lu et al. 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. 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.

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.

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.

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.

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