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Stem Cells Advances in Ophthalmology: A Review

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ABSTRACT

Vision is one of the most valuable senses humans have. However, there are quite a few clinical conditions that threaten and compromise its function. Advances in the development of therapeutic strategies have led us to use stem cells to treat from chronic-degenerative pathologies to infectious-contagious diseases. Taking this into account, it is of vital importance to evaluate the possibility of future therapeutic strategies using stem cells to treat and manage ophthalmic pathologies.

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INTRODUCTION

Vision is one of the most useful senses and considered to be practically irreplaceable. If lost, it could impose a great amount of consequences and changes in the life of the person affected acknowledging that this event represents a significant risk factor for depression among older adults.(1)

There are several pathologies that, directly or indirectly, end up causing damage to the eye and all its components. Damage that can, in some cases, be irreversible, giving the patient very poor prognosis and little to none possibilities of recovery. Therefore, nowadays, it has become a need to implement fruitful therapies to stop the progression or even reverse the damage caused by these conditions. The knowledge of the theoretical role of stem cells as therapy allows us to contemplate the possibility of implementing them to find a way to treat ophthalmological diseases that in other scenarios could be impossible to achieve or even consider. Stem cells are defined as precursor cells that have the capacity of self-renewal and differentiation to generate diverse mature cell types with specific functions. There are three main types of stem cells useful in ophthalmic therapy due to their potential affinity to ocular tissues: human embryonic stem cells (hESC), human-induced pluripotent stem cells (hiPSC) and mesenchymal stem cells (MSC). In this review the last two out of the three are going to be discussed.

Stem cells, what are they?

Stem cells are those known to have a remarkable and unique potential to renew themselves. They have the ability to differentiate into many different cell types during early life and growth stages. The two defining characteristics of a stem cell are perpetual self-renewal and the ability to differentiate into a specialized adult cell type. (2)

The main focus of this article will be stem cells that enter in one of these four main categories: Embryonic, pluripotent, mesenchymale and induced stem cells.

Embryonic stem cells are immortal and are totipotential, in other words, thes units of life can develop a whole human if they get nutrients. (3)

Pluripotent stem cells have the ability to undergo self-renewal and to give rise to all cells of the tissues of the body. (4)

Multipotent (Mesenchymal) stem cells have the ability to differentiate into all cell types within one particular lineage. (5)

Human induced pluripotent stem cells (hiPSCs) are somatic cells reprogrammed to a state with more self renewal and differentiation potential. (6)

Stem cells are undifferentiated cells in multicellular organisms, which have the ability to differentiate into multiple lineages. Stem cells possess unlimited potential to replenish when there is a need to repair the tissues and organs in our body. (7)

Ophthalmological genetic syndromes and stem cells

Stem cells for treatment of retinitis pigmentosa.

Retinitis pigmentosa (RP) is a genetic disorder that can cause blindness with external retinal degeneration. The onset is with a sudden loss of night vision, followed by peripheral vision, and sometimes ends in a complete loss of vision. Although retinal hyperpigmentation is a strong landmark of

the disease, the cellular and molecular mechanisms underlying this phenotype remain unclear. The hypothesis for the development of RP is a rod-cone dystrophy, with the consequent degeneration of the rods that precede the cones and, finally, atrophy of the RPE of the retinal pigment epithelium [8,9].

There are some studies that strongly suggest that the RPE cells are more affected in splicing factor mutations, such as pre-mRNA processing factors 3, 8, and 31 (PRPF3, PRPF8, and PRPF31). [10]

RPE is a single-layer barrier between the choroidal blood vessels and the sensorial retina. Photoreceptor cells are totally dependent on RPE. The obtaining of ATP due glucose utilization, synthesis of proteins, and removal of metabolic waste is a function and takes place on RPE [8].

There are treatments available to slow down the progression of this condition. There are several novel approaches aimed at preventing the course of photoreceptor loss, such as growth factor injections, gene therapy, and some cell-based therapies.[8]

Umbilical cord Wharton's gelatin derived mesenchymal stem cells (WJ-MSCs) have important paracrine and immunomodulatory role, as well as excellent stimulant influence on RPE or the production of trophic factors that are similar to those produced by RPE. It has been discovered that WJ-MSCs can be used to prevent the progression of retinal destruction and to attempt to render photoreceptors that are in the inactive phase intact.[8]

WJ-MSCs have been shown to suppress chronic inflammation and prevent apoptosis in animal models of neurodegenerative and ischemic retinal disorders. WJ-MSCs also stimulate progenitor cells in the retina and elicit self-repair mechanisms.[8]

Mesenchymal stem cells (MSCs) have been reported to be useful in various treatment options because they can produce a wide range of regenerative, anti-inflammatory factors, prevent apoptosis, and fibrosis. It's also known that WJMSC has effects on the ability to inhibit T cell proliferation [8,11]

Regardless of the genetic alteration, the administration of sub-spike WJ-MSC appears to be a very viable option. There are no reports of ophthalmologic or systemic unwanted effects. Although the long-term side effects are still unknown. Various studies have shown the ability of RPCs to differentiate into various retinal neurons and glial cells, but this is limited after transplantation, as this process of cell integration and differentiation is completely dependent on the host environment, including the maturity of the retina, the immune response and inhibitory molecules secreted by the damaged retina. [12]

Stem cells for treatment of Usher Syndrome.

Usher syndrome is the most prevalent form of syndromic presentation of retinitis pigmentosa and includes types I, II (more than half of the cases), and III with their respective varying degrees of hearing loss [13-16].

The retina in Usher syndrome shows exactly the same findings as in nonsyndromic retinitis pigmentosa. The Stem Cell Ophthalmology Treatment Study (SCOTS) and the second and subsequent Stem Cell Ophthalmology Treatment Study II (SCOTS2) are clinical trials currently using autologous MSCs to treat various optic diseases. Patients have shown substantial improvements in visual function, including those related to acuity and peripheral vision. One patient demonstrated slight improvement in both decibels and word comprehension after the procedure. This is theoretical, suggesting that the cells that are responsible for the translation of hearing signaling are related in a similar way by mutations in the gene [13].

Likewise, the coupling of the CRISPR / Cas9 system together with the patient-specific hiPSC technology has shown a window for regenerative therapy and personalized medicine for hereditary retinal dystrophies [14], which is especially important in this type of disease, where point changes in coded regions. , make the individual gap huge. The results of improvements in several inherited retinopathies and optic neuropathies demonstrated through studies suggest that the mechanisms of action of MSCs may improve residual visual damage caused by deleterious genetic mutations. [13]

Stem cells for treatment of AMD.

Age-related macular degeneration (AMD) has become the leading cause of vision loss in elderly people, especially persons older than 75 years of age in the United States [14].

This is explained due to dysfunction and loss of retinal pigment epithelium cells and photoreceptors that lead to worsen acuity in patients with non-neovascular AMD.[15-17]

The use of hiPSCs for the treatment of AMD is encouraging and holds great potential, but there are still important obstacles that if not resolved, can have deleterious results; hiPSC technology has offered fresh knowledge, as well as understanding about retinal degeneration through autologous iPSC development and disease modeling [14,15].

It is important to optimize developing more efficient methods to produce large numbers of cells ready for clinical use, as well as, offering safety and integrity to the patients, letting us understand the long-term survival profiles of cells post-transplantation [14].

At the present, it may be amenable to hESC-based cell therapy for treating AMD. The results of a phase 1 clinical trial provided an early indication about safety of manufacturing an hESC monolayer on a synthetic basement membrane for delivering as patch for treatment for AMD [17].

Stem cells for treatment of Stargardt disease.

Stargardt disease is an autosomal recessive retinal disorder characterized by a predominantly juvenile macular dystrophy associated with central visual impairment and progressive

bilateral atrophy of the retinal pigment epithelium and is caused by mutations in the ABCA4 gene. [18,19]

Subretinal transplantation of retinal pigmented epithelial cells derived from human hESCs is emerging as a therapeutic possibility, using Yamanaka factors. There is evidence of complement dysregulation manifested by elevated C3 / C3b / iC3b deposition and MAC using these therapies; these findings strongly support an inflammatory etiology, for these reasons it is necessary to continue improving to offer safety [19,20].

Ophthalmological surgery and stem cells

Applications of stem cells in oculoplastic surgery and regulation.

At the present time, over 180,000 corneal transplants are performed in ophthalmology surgical centers every year, and have become the most frequent form of tissue grafting. In low-risk corneal transplants, where there is no vascularization or inflammation, 5-year graft survival rates exceed 90%.[21-22]

However, in those with a history of rejection against it, or marked vascularization in inflammation, more than 50% of the grafts fail [23,24]. Here is where the need of finding a way to reduce these high rejection rates is born.

It has been investigated the role of systemically injected MSCs in corneal transplantation. The researchers formed MSCs directly from the bone marrow of wild-type BALB/c or GFP C57BL/6 mice, after that, injected these cells into allograft recipients intravenously at a 3 hour following surgery. GFP+ MSCs were found in the transplanted cornea and ipsilateral conjunctiva, as well as lymph nodes, but were not present in the contralateral ungrafted tissues. [25]

Therapy with MSCs limited allosensitization, has shown significantly reduced frequencies of mature MHCII+CD11c+ APCs in the close draining lymph nodes relative to control recipients. An attendant reduction in IFN-γ+ Th1 effector cells was found in the MSC-injected allograft recipients compared to the controls. MSC-injected allograft recipients exhibited prolonged allograft survival relative to control allograft recipients [25].

Also, has been used in a murine model of corneal transplantation [25,26]. In their study, they were able to prolong corneal allograft survival with the following intravenous infusion of MSCs.

The faculty of MSCs to induce and modulate corneal allograft survival has been substantially demonstrated by the immune response in a rat model of corneal transplantation [27]. The report shows that in addition to suppressing the Th1 pro-inflammatory response, treatment with MSCs considerably upregulated Tregs with increased frequencies of lymph node and splenic CD4+CD25+Foxp3+ Tregs and augmented Foxp3 mRNA expression compared to vehicle-treated controls. [27]

These alterations to the effector and regulatory arms of the immune response can be explained by prolonged graft survival time in rats that received postoperative injection of MSCs relative to controls. The expansion of splenic CD4+Foxp3+ regulatory T cells in MSC-treated animals in a rat model of corneal transplantation has also been reported.[28]

In their study, investigators assessed the ability of MSCs from three different sources to promote allograft survival. A completely allogeneic transplantation design was used, with Lewis rat recipients and Dark Agouti donors. Recipient rats were treated intravenously with MSCs from Lewis rats (syn), Dark Agouti rats (allo) or Wistar Furth (third party). Corneal allograft survival was consistently prolonged in allo-MSC treated and third-party MSC treated allograft recipients, with 90% and 80% survival respectively at 30 days after transplantation. In comparison, 80% of grafts in untreated recipients were rejected, and intriguingly, 100% of grafts in syn-MSC treated allograft recipients were rejected. In addition to expanded splenic CD4+Foxp3+ Tregs in the alloand third-party MSC treated animals, the authors report diminished corneal infiltration of NK T cells in these groups.These studies strongly suggest that MSCs are a viable strategy for promoting corneal allograft survival.

Corneal epithelial maintenance and regeneration are performed by a subpopulation of stem cells residing at the limbus, the border area between the cornea and conjunctiva [29, 30]. Limbal stem cell deficiency is defined as a complete or partial loss or dysfunction of LSCs that can be the result of diverse medical conditions, for example, chemical or thermal burns, long-term contact lens wear, as well as autoimmune diseases such as Stevens-Johnson syndrome or ocular cicatricial pemphigoid, or genetic diseases like aniridia [29]. Patients with LSCD are not able to maintain the corneal epithelium, with the resulting worsening of the loss of anti-angiogenic privilege and ingrowth of conjunctival epithelial cells. invariably, this situation leads to neovascularization of corneal stroma and corneal opacification with the resulting significant vision loss [29]. Limbal stem cell transplantation (LSCT) is the definitive treatment for total limbal stem cell deficiency [31]. The amniotic membrane is a unique technique that combines properties that include facilitation cellular migration, reinforcement of basal cellular adhesions, encouragement of epithelial differentiation, modulation of stromal scarring, and inflammatory suppressing activities [31]. Consistent data has shown that both LSCs and corneal epithelial cells contribute toward closure of corneal wounds. In wild-type mice, removal of the limbal rim delayed closure of 1.5-mm wounds, and not of 0.75-mm wounds, indicating that smaller wounds do not rely on LSCs as do larger wounds [30]. Due to these properties, it is remarkable the fact of using these therapeutics for improvement of limbal stem cell deficiency, diminishing further complications of surgery.

CONCLUSION

The main objective of our bibliographic review was to show which treatments in the matter of stem cells are considered

suitable for the various pathologies that afflict the eyes, in addition to evoking those treatments that were created optimal against selected pathologies, or that showed benefits .

The authors of this text consider the question of selecting the appropriate strategies of vital importance, literally, since choosing the therapy to be used in a patient is the turning point in what kind of quality of life he leads, or if he leads one at all. We argue that even if there is only one patient with an eye condition, it would be no less important to invest efforts in using the correct compound, however, the situation distresses the health of an important part of humanity, and virtually a growth in the statistics of the infected population in its vision due to various pathologies.

For all the arguments put forward in the preceding lines, we justify the need for this product.

Regarding the bibliography selected for the elaboration of this work, we find it refined, each one of the articles that compose it, whether those of bibliographic review or those of experimental studies, have the necessary methods for their correct mission. Regarding the "confrontation" of the information at the time of conducting this review of bibliographic sources, we did not find discrepancies, instead some validated the others, and vice versa.

Properly speaking, our aim is to present hard data on the current trend in stem cells.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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