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Stem cell therapies in ophthalmology

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ABSTRACT

Stem cells have been used for therapeutic purposes in many areas of medicine for many years. Depending on the tissues from which they are derived and their characteristics, stem cells can be classified into various groups. Some types of stem cells have the capacity to form an entire organism, while others can only differentiate into certain groups of tissues. In recent years, stem cells have also become popular in ophthalmology. Both stem cells found in ocular tissues and those derived from peripheral tissues are gaining attention for their use in ophthalmology. In ophthalmology, stem cells have a wide range of applications, from ocular surface and periocular tissue applications to retinal diseases. Some applications, such as limbal stem cell transplantation, have become common practices in clinical settings, while experimental and promising stem cell methods, such as anterior chamber stem cell transplants or subretinal supracoroidal stem cell transplants, are being investigated. Stem cells offer hope in ophthalmology for diseases that are unresponsive to traditional treatments, irreversible diseases, or dystrophic diseases that still lack approved treatments. The long-term effects of stem cell transplants in ophthalmology have not been clearly established, and the potential for tumor development due to uncontrolled proliferation has not been entirely eliminated. While there is a possibility of negative results from experimental studies and the emergence of concerning side effects, stem cells still hold promise as an alternative treatment option in ophthalmology.

Keywords: Ocular surface, ophthalmology, regeneration, retina, stem cell

INTRODUCTION

Stem cells are undifferentiated cells found in embryonic, fetal and adult tissues. They possess the properties of self-renewal, clonality and differentiation.[1] Although there are different classifications, stem cells can broadly be divided into three groups: embryonic stem cells (ESC), mesenchymal stem cells (MSC) and induced pluripotent stem cells (iPSC). While ESCs have a high capacity for self-renewal and differentiation, the ability of stem cells in adult tissues to self-renew and differentiate is limited. Therefore, ESCs can form an entire organism containing different tissue types, whereas adult tissue stem cells can only differentiate into limited cell or tissue types. ESCs originate from the blastocyst and exhibit pluripotent characteristics in terms of their differentiation capacity.[2] The high differentiation capacity of ESCs enables them to transform into various cell types in damaged ocular tissues. In the developing organism, some progenitor cells do not differentiate into terminal tissues and remain as tissue stem cells, which are called MSCs. Tissue stem cells in different tissues exhibit diverse behaviors. In tissues such as the heart, pancreas, and nervous system, tissue stem cells that can proliferate in response to tissue damage remain quiescent otherwise. However, in some tissues like bone marrow, liver, digestive system, and adipose tissue, they not only respond to tissue damage but also play a role in normal tissue turnover. In ophthalmological diseases, MSCs derived from adipose tissue and bone marrow are more commonly used. Especially, MSCs from adipose tissue are preferred because they can be easily obtained from subcutaneous fat tissue.[3] iPSCs are stem cells produced from adult somatic cells that exhibit functions similar to ESCs. Human iPSCs were first produced by Yamanaka and his colleagues.[4] The advantage of iPSCs is that they eliminate the need for a donor since they can be used autologously, and like ESCs, they have a broad differentiation capacity. However, their use is limited due to the unpredictability of complications such as tumor formation associated with genetic instability.[5]

Stem cells support tissue regeneration in target tissues and exhibit anti-inflammatory, immunomodulatory, proangiogenic and antiangiogenic, anti-apoptotic, and anti-aging effects. Stem cell therapies were first used in the 1950s and have been tested in almost every field of medicine.[6] In terms of eye diseases, stem cell treatments are being tried in degenerative diseases that result in irreversible cell damage and in tissue damage caused by mechanical, chemical, or thermal traumas, where conventional treatments have not been satisfactory. Some study results are promising. Stem cell therapies have found a wide range of applications in ophthalmology, from periocular stem cell applications to inherited retinal diseases. The small amount of stem cells required for application and the immune privilege of the eye make stem cell therapies easier

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to implement.[7] Stem cells can be applied to the eye as topical drops, through amniotic membrane, or using scaffolding tissues produced by bioengineering studies. Additionally, there are subconjunctival, intrastromal, intracameral, intravitreal, suprachoroidal, and systemic applications available. Although exciting results have been obtained in studies, widespread clinical applications of stem cells that have been approved by local authorities are still not available. Moreover, the costs of stem cell applications and the unknown long-term outcomes of treatments also limit the use of stem cell therapies. In this review we will discuss the use of stem cells in ophthalmological diseases.

OCULOPLASTY AND PERIOCULAR DISEASES

Stem cell applications around the eyes have gained popularity primarily for cosmetic and anti-aging purposes. Hyaluronic acid and collagen are widely used for cosmetic purposes. Recent studies have shown that wrinkles around the eyes decrease, and eyelids regain their former appearance after the injection of autologous adipose-derived stem cells.[8] In addition to cosmetic applications, stem cell treatments can also be applied to periocular tissues and eyelids in cases of tissue defects caused by various mechanical traumas, non-healing wounds, and burn-related injuries. In the past two decades, MSCs have been frequently tested for deep skin burns. In some centers in our country, case reports have been presented where fat tissue-derived stem cell treatments following severe facial burns led to the recovery of the eyelids in a way that allowed them to maintain normal function.[9] The main pathology in non-healing wounds is impaired tissue circulation and uncontrolled release of inflammatory agents. Stem cells, with their anti-inflammatory effects, can promote wound healing by providing immunoregulation and regulating vascularity in skin tissues.[10] In chronic wounds of the periorbital skin, stem cells can be an effective alternative in addition to traditional treatments. To optimize the effectiveness of stem cells in tissue defects, bioengineering studies have emerged. Biomaterials have been developed to serve as an extracellular matrix for stem cells.[11] The use of these biomaterials has increased the efficacy of stem cells in target tissues and improved tissue healing levels.

CORNEA AND OCULAR SURFACE DISEASES

In corneal and ocular surface diseases, the most popular stem cell applications are limbal stem cell transplantation and, although not a direct stem cell application, amniotic membrane transplantation. The amniotic membrane is separated from the placenta by blunt dissection after washing the placenta, obtained from an elective cesarean section, with various antibiotics. The epithelial surface is placed upward on nitrocellulose paper and cut to the required size. It is then stored in sterile containers containing glycerol at -80°C. The amniotic membrane graft is placed on the relevant ocular surface with the epithelial side facing upward and fixed with sutures of various sizes. The amniotic membrane, containing growth factors, accelerates tissue healing, enhances epithelial regeneration, and reduces scar formation.[12] Due to these properties, it is widely used in cases such as non-healing corneal ulcers and infections. Recently, the amniotic membrane has also been used as a carrier for stem cell therapies on the ocular surface.[13] Limbal stem cell deficiency can occur in diseases with systemic mucosal involvement, such as Stevens-Johnson Syndrome, chemical or thermal eye burns, or mechanical trauma. Limbal stem cells play a crucial role in maintaining the continuity of the corneal epithelium and its regeneration capability, and their deficiency can lead to severe vision loss.[14] In patients with unilateral eye involvement, autologous limbal stem cell transplantation can be performed from the other eye. In cases of bilateral involvement, allogeneic limbal stem cell transplantation from close family members can be performed.[15] Applications of cultured limbal stem cells have also shown successful outcomes.[16] As an alternative to limbal stem cells in ocular surface diseases, MSCs derived from adipose tissue or bone marrow are used. The most commonly used method in limbal stem cell transplantation is the simple limbal epithelial stem cell transplantation method. In this technique, a minimal amount of limbal tissue is taken from the donor eye and applied to the recipient eye's cornea, with the cornea being covered by an amniotic membrane. The covering of the cornea with the amniotic membrane facilitates the effective in vivo spread of the transplanted stem cells. The simple limbal epithelial stem cell method eliminates the need to take large amounts of tissue from the donor. The advantage of these stem cells is that they are easily obtainable, eliminating donor limitations.[17]

Additionally, iPSCs are being investigated for use in corneal diseases. iPSCs can form the three different cellular layers of the cornea: epithelium, stroma, and endothelium. These properties make stem cells a promising alternative treatment for full-thickness corneal diseases requiring transplantation and for corneal dystrophies.[18] Intrastromal MSC applications are also being studied in relatively common corneal diseases like keratoconus, and the initial results appear promising. Increased stromal collagen production has been reported after intrastromal stem cell application in patients with keratoconus.[19] In patients with dry eye disease, treatments involving the application of topical drops containing MSCs to the ocular surface and the injection of stem cells into the lacrimal gland have shown successful results.[20] Studies have also shown that in patients with bullous keratopathy, corneal clarity was restored, and there was a significant increase in corneal endothelial cells after injections of cultured human corneal endothelial cells into the anterior chamber.[21] Stem cell therapy is also being explored for the treatment of corneal opacities caused by mucopolysaccharidoses, as well as for the treatment of corneal scars and neovascularization due to various causes, with promising results.[22]

GLAUCOMA

Glaucoma is one of the leading causes of permanent vision loss worldwide. It is a progressive optic neuropathy characterized by the loss of retinal ganglion cells. The most significant risk factor for glaucoma is elevated intraocular pressure (IOP). Traditional treatments for glaucoma have focused on regulating IOP. Both topical drops and various systemic medications are widely used as antiglaucoma treatments. Additionally, various laser therapies and surgical methods for glaucoma are applied in patients with limited response to medical treatment.[23] While these widely used treatments effectively lower IOP, retinal ganglion cell damage remains irreversible and untreated. In some patient groups, cellular damage continues to progress despite all these treatments. Stem cell applications in glaucoma

patients have primarily focused on two areas: first, the retinal ganglion cell damage and neuropathy that result from all types of glaucoma; and second, the dysfunction of human trabecular meshwork cells, which plays a role in the pathophysiology of primary open-angle glaucoma. Since traditional treatments cannot reverse cell damage, alternative therapies capable of cell regeneration and slowing the progression of neuropathy have been sought. Currently, there is no accepted neuroprotective treatment for glaucoma. Various stem cell studies have shown that retinal ganglion cell neuroprotection can be achieved. It has been demonstrated that the most critical factor in retinal ganglion cell damage in glaucoma is the lack of neurotrophic factors, and that stem cell application provides neurotrophic factors at levels sufficient to reduce ganglion cell damage.[24] ESCs, iPSCs, and MSCs have each been tested in the treatment of glaucoma-related neuropathy. While human studies are limited, promising results have been obtained in experimental animal models.

In the pathophysiology of primary open-angle glaucoma, resistance to aqueous outflow in the trabecular meshwork plays a role.[25] Experimental studies have shown improvement in trabecular meshwork function following the injection of adipose-derived MSCs into the anterior chamber.[26] Similarly, the introduction of iPSC-derived trabecular meshwork cells into the anterior chamber has been found to improve trabecular meshwork function.[27] In stem cell applications for glaucoma patients, bone marrow-derived and adipose-derived MSCs are more frequently preferred due to their easy accessibility and the possibility of autologous application. These stem cell studies, which could provide an alternative for the treatment and control of glaucoma progression, are currently limited to animal experiments, and data on their long-term effects and safety remain limited.

RETINAL DISEASES

The retina is a crucial component of the visual function, as it processes the image received by the eye and transmits it to the central nervous system. Numerous systemic diseases and medications can affect retinal tissue. Among the systemic diseases that affect the retina, diabetes is the most prominent. Diabetic retinopathy (DR) is considered one of the degenerative retinal diseases, along with various other retinal disorders. Degenerative retinal diseases are characterized by irreversible cell damage in the retina, which has a multilayered structure. The leading disease in this group is age-related macular degeneration (AMD), which is the most significant cause of irreversible vision loss in individuals over 60 years of age in developed countries. AMD is classified into two types: neovascular and non-neovascular. In a specific subset of patients, intravitreal anti-vascular endothelial growth factor injections can control the disease to some extent, but both dry and wet types can ultimately result in geographic atrophy or scar tissue formation due to neovascularization. Some biologic agents recently approved by the FDA for geographic atrophy have been introduced, but treatment options remain limited once irreversible damage occurs. Retinitis pigmentosa (RP), Stargardt disease (SD), and other retinal dystrophies are also included in the group of degenerative retinal diseases, with no established treatments currently available to halt or reverse the degenerative process. Given the irreversible and progressive nature of retinal diseases and the limitations of traditional treatments, stem cell therapies have emerged as an alternative and highly researched field. Gene therapies, which also hold great potential for degenerative retinal diseases, are a subject of their own.

In DR, traditional treatments include laser photocoagulation, anti-VEGF agents, steroid implants, and vitrectomy. However, in some patients, neovascularization and progressive retinal cell damage continue despite these treatments. Stem cell therapies in DR primarily aim to limit neovascularization and restore retinal cell damage. In experimental models of DR in mice, the injection of endothelial progenitor cells derived from healthy humans showed improvements in retinal microvascular damage in both acute and chronic vascular injury.[28] Studies have also demonstrated that the application of photoreceptor cells derived from ESC can improve photoreceptor cell function in the target tissue. Additionally, adipose-derived stem cells and other MSC therapies have been investigated for their potential to restore both vascular damage and retinal cell damage in DR, with some studies yielding positive results.[29]

In AMD, stem cell therapies have focused primarily on restoring and replacing the retinal pigment epithelium (RPE). To this end, retinal stem cells obtained from donor retinas, induced pluripotent stem cells (iPSCs) that differentiate into RPE cells, and human ESCs have been used. The first transfer of RPE cells in humans was performed by Peyman and colleagues.[30] Although the initial applications resulted in significant complications, this study was a major milestone for future research. Today, various autologous and allogeneic stem cell studies continue intensively in AMD, with ESCs and iPSCs being preferred, while trials with MSC have led to relatively more complications. Moreover, in stem cell applications for AMD, subretinal application has been preferred over intravitreal application, but this method is more invasive and prone to complications.[31]

Stem cell applications also hold significant interest as a research area in hereditary retinal diseases. RP, SD, and many other hereditary retinal diseases currently lack an accepted treatment. Gene therapies and stem cell treatments are promising in this group of diseases. The general goal of stem cell treatments in hereditary retinal diseases is to prevent cell apoptosis and restore damaged cells. ESCs, iPSCs, and MSCs have been tested in various studies. Several stem cell studies, particularly for RP and SD, have been conducted and are ongoing in Turkey.[32,33] Long-term stem cell treatment in RP has been shown to provide only limited improvement. Furthermore, in addition to intravitreal and subretinal stem cell applications, supracoroidal injection has recently been described. This newly defined method is less invasive thanks to the use of micro-needles, and the injection contents exhibit a longer-lasting effect in the supracoroidal space. In subretinal application, after performing pars plana vitrectomy, varying amounts of stem cells are injected into the subretinal space around the damaged tissue. The widely used technique for supracoroidal application is the Limoli retinal restoration technique. In this technique, the globe is deviated superonazally, and a sclerotomy is performed until the choroidal color is visible in the inferotemporal region. The tissue carrying the stem cells is placed onto the choroid, and the scleral flap and the tissues above it are sutured appropriately.[34] Another research area in stem cell studies for retinal diseases involves the development of three-dimensional retinal organoids from iPSCs and their use to achieve functional capacity in the target tissue.[35]

OPTIC NEUROPATHIES

Optic neuropathies are a broad group of disorders characterized by impaired optic nerve function and optic nerve abnormalities. While they may primarily be related to the optic nerve itself, optic neuropathies can also develop secondary to infectious, inflammatory, and various systemic diseases. Glaucoma, discussed in previous sections, is one of the leading causes of optic neuropathy. In addition to systemic causes, there are also hereditary optic neuropathies. The most common hereditary forms include Leber's Hereditary Optic Neuropathy (LHON) and Autosomal Dominant Optic Atrophy (ADOA). A common feature of all these diseases is retinal ganglion cell damage. Causes of demyelinating optic neuropathy include neuromyelitis optica (NMO), multiple sclerosis (MS), and other autoimmune demyelinating diseases.[36] In an experimental study involving patients with NMO, systemic clinical improvement was observed after intravenous MSC application, along with an increase in RNFL thickness.[37] Additionally, there are studies in NMO patients where peripheral hematopoietic stem cells have been tested. LHON is a mitochondrial disease characterized by retinal ganglion cell damage due to oxidative stress. To reverse mitochondrial dysfunction in LHON, iPSCs and bone marrow-derived stem cells have been tested in humans, with reported improvements in visual acuity.[38]

Non-arteritic anterior ischemic optic neuropathy (NAION) is one of the most common acute optic neuropathies, with acute ischemia-induced optic nerve damage as the underlying pathophysiology. Various types of stem cells and different administration methods have been tested in mouse models of NAION, with positive results obtained.[39] Additionally, a clinical study involving NAION patients showed improvement in visual acuity in the majority of participants.[40] Traumatic optic neuropathy is the irreversible damage to the optic nerve caused by various types of trauma. In experimental mouse models and some human studies, stem cell applications have.[41]

STEM CELL SOURCES FOR OPHTHALMIC USE

Stem cells used in ophthalmological treatments can be obtained from ocular tissues, peripheral blood, bone marrow, adipose tissue, and embryonic tissues. Ocular tissues contain stem cells in the cornea, conjunctiva, trabecular meshwork, ciliary body, lens, retina, and choroid. Stem cells are found in the Vogt palisades of the corneal limbus. Limbal stem cells play a role in the regeneration of the corneal epithelium and are commonly used in cases of limbal stem cell deficiency.[42] The anterior stroma of the cornea also contains stem cells. The stem cells located in the corneal stroma play an important role in maintaining the organization and transparency of the cornea. The therapeutic use of these stem cells is limited to laboratory studies.[43] Conjunctival stem cells are located in the bulbar conjunctiva and can be frequently used in ocular surface disorders.[44] Iris pigment epithelial cells exhibit stem cell activity, and experimental studies on the use of these stem cells are ongoing. Stem cells have also been identified in the ciliary body and trabecular meshwork, and research on their use is in the experimental phase.[45-47] The lens capsule contains stem cells that play a role in maintaining the transparency of the lens, and their deficiency can lead to cataracts and other lens pathologies.[48] Retinal pigment epithelial (RPE) cells exhibit stem cell activity. Abnormalities in RPE cells play a role in the pathophysiology of various retinal diseases, such as retinal dystrophies, RP, and AMD. Retinal stem cell transplants are frequently used in retinal dystrophies and degenerative retinal diseases.[49]

In addition to stem cells obtained from ocular tissues in ophthalmology, other types of stem cells obtained from different tissues can also be used. Induced pluripotent keratinocytes (iPKH) are obtained from adult somatic cells and can be transformed into corneal epithelial cells, RPE cells, photoreceptor cells, and retinal ganglion cells using various transcription factors, making them useful for ophthalmological diseases.[50] Although human studies are limited, and the possibility of tumor development in the long term cannot be predicted, research continues as a promising alternative treatment. MSC derived from adipose tissue can be easily and minimally invasively obtained from peripheral adipose tissue, including fat tissue from the eyelid, during eyelid surgery.[51] These adipose tissue-derived stem cells exhibit MSC activity and can be applied periocularly, to the ocular surface, and intraocularly. Hematopoietic stem cells, bone marrow-derived stem cells, central nervous system stem cells, and ESCs are also used as sources of stem cells. Stem cells used in each ophthalmological disease represent a broad field of research, and studies on the use of stem cells in ophthalmological diseases continue to increase worldwide. Although the unpredictability of long-term effects remains the biggest concern, stem cells appear to be a promising part of future clinical practice in various ophthalmological diseases.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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