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Review

Recent advances in stem cell-based therapeutics in ophthalmology

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ABSTRACT

Ophthalmology is a medical discipline that examines and treats eye diseases. Research conducted in this field indicates a significant advancement in the use of stem cells for the treatment of retinal diseases. Stem cell applications, successfully employed in various medical branches, emerge as a hopeful prospect for the treatment of specific eye conditions. Retinal diseases, particularly age-related macular degeneration, Stargardt's macular dystrophy, and retinitis pigmentosa encompass widespread eye conditions leading to vision loss. At present, there is a lack of effective methods for treating these diseases. Therefore, stem cell therapy is being investigated as a promising alternative. Stem cells obtained from different sources can be used for this treatment. Clinical studies in this field indicate that the applied therapy could be effective in treating retinal diseases. However, the standardization of stem cell therapy, examination of long-term outcomes, and a more detailed assessment of potential complications are necessary. This review aims to examine the development of studies conducted in the field of ophthalmology from the past to the present and highlight the impact of these studies on eye health and clinical applications. Simultaneously, it aims to contribute to the development of a better understanding and more effective treatment options in the fight against eye diseases by inspiring future research.

Keywords: Embryonic stem cells, induced pluripotent stem cells, macular degeneration, ophthalmology, stem cell therapy.

Embryonic stem cells (ESCs), first isolated from mouse embryos in 1981, marked a significant milestone in laying the foundation for stem cell research. The isolation process enabled the expansion of ESCs in culture conditions and their differentiation into various cell types. This has allowed scientists to differentiate ESCs into numerous tissues and cell types for tissue repairs, treatments, or research. Embryonic stem cells hold great potential in medical research and therapy, particularly garnering interest as cell sources for treating degenerative diseases and tissue regeneration. However, ethical and legal considerations regarding the use of ESCs remain prominent issues.[1] The isolation of human ESCs was first achieved under laboratory conditions in 1998.[2] By 2006, adult stem cells (ASCs) were successfully reprogrammed to exhibit characteristics similar to ESCs, leading to the introduction of a new type of stem cell known as induced pluripotent stem cells (iPSCs).[3] Human studies began in 2009 with the approval of the Food and Drug Administration (FDA). One of these studies investigated the treatment of spinal cord injuries using iPSCs.[4] Stem cells are specialized cells with the unique ability to undergo unlimited self-renewal and differentiate into various cell types.[5] Progenitor cells can be defined as versatile cells with the ability to self-renew. The term 'stem cell' encompasses progenitor and precursor cell types. Various mature cell types can emerge from stem cells with high proliferative capacity. They can proliferate in a suitable environment and differentiate into other cells, thus contributing to the continuous renewal of the tissue. Additionally, stem cells possess the ability to repair damaged tissue and restore dysfunctional tissue in the body.[6] Due to these characteristics, stem cells can play a significant role as a treatment option in conditions such as eye-related degenerative retinal diseases, limbal stem cell deficiencies, and glaucomatous ganglion cell injuries. The eye stands out as an advantageous field for stem

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cell therapies compared to other organs. These advantages include: Firstly, the quantity of stem cells required in the eye is less than in other organs, reducing the cost of treatment. Secondly, stem cell transplantation in the eye can be applied more easily from a surgical perspective.[7] Thirdly, cells transplanted with imaging methods in the clinic can be more easily monitored and controlled within the eye. Finally, due to the eye's unique immune privilege, there is no need for long-term immunosuppressive treatment. Experimental studies based on stem cells demonstrate that the application of healthy stem cells in place of degenerated retinal cells significantly contributes to the restructuring of retinal tissue, the formation of new cell connections, and the improvement of visual function.[8] These studies indicate that stem cells have the potential to differentiate into various cell types found in the retina. Particularly in previous experimental studies, the ability of stem cells to adapt to retinal neural cells such as Müller, amacrine, bipolar, horizontal cells, and photoreceptors has been noteworthy.[9] Therefore, stem cell-based treatments may serve as a significant source of hope as a potential solution for degenerative retinal diseases. In the treatment of retinal diseases, ESCs, iPSCs, and mesenchymal stem cells (MSCs), especially those derived from bone marrow and adipose tissue, are being utilized.[10] These different types of stem cells hold promising potential for retinal treatment. Stem cells are categorized into three based on their properties:

Proliferation:

A stem cell has the ability to divide and multiply over extended periods. This involves the capability of the stem cell to renew itself multiple times.[11]

Self-renewal:

After division, a stem cell has the ability to maintain the characteristics of the newly formed cells. In other words, when stem cells divide, the resulting cells can retain stem cell properties like the previous cell.[12]

Differentiation:

Undifferentiated stem cells have the capacity to transform into other cells with specific functions. This transformation process is influenced by both internal and external factors. Internal factors are controlled by the cell's own genetic information. External factors, on the other hand, are regulated by chemical factors released by other cells in the surrounding environment, physical contact with neighboring cells, and other molecules present in the environment. These factors can influence the transformation of stem cells into a specific cell type.[13]

STEM CELL TYPES

Stem cell types vary based on their sources and acquisition methods.

1. Embryonic stem cells

Embryonic stem cells are cells isolated from the mass of cells called the blastocyst within the first 3-5 days of the embryo and cultivated under laboratory conditions. These specialized cells possess pluripotent characteristics, meaning they have the ability to differentiate into cells of ectodermal, mesodermal, and endodermal origin in the body.[14] Therefore, ESCs can function across a broad spectrum of differentiation potential. An important advantage of ESCs is that they can be obtained without harming the embryo. This provides researchers with the opportunity to ethically and legally obtain these valuable stem cells. Embryonic stem cells hold significant potential in the field of regenerative medicine for the treatment of diseases and tissue regeneration.[15]

2. Adult stem cells

Adult stem cells are undifferentiated cells found in various tissues of the adult organism and can be obtained under laboratory conditions. These cells can be present in different body tissues, such as blood, blood vessels, skeletal muscle, skin, teeth, bone marrow, adipose tissue, and cartilage. The most common sources of ASCs are adipose tissue and bone marrow. A subtype of ASCs known as MSCs is a significant stem cell type obtained from these tissue sources. Mesenchymal stem cells have the ability to differentiate into many undifferentiated cell types in the body.[16] Therefore, they are considered “multipotent” in terms of differentiation potential. This means that these cells can differentiate into specialized cells in different tissues but do not have as broad a differentiation potential as pluripotent stem cells. Mesenchymal stem cells play a significant role in regenerative medicine applications and

tissue engineering. These cells can be used in many medical applications, such as tissue damage repair, and bone and cartilage regeneration, in the field of regenerative medicine and tissue engineering.[17]

3. Induced pluripotent stem cells

Induced pluripotent stem cells are a type of cell obtained by genetically reprogramming cells taken from the adult organism under laboratory conditions to acquire characteristics similar to ESCs. Stem cells of this type possess pluripotent characteristics, meaning they have a broad potential for differentiation, similar to ESCs. Induced pluripotent stem cells are obtained by reverting the specialized cell characteristics of cells taken from the adult organism.[18] This reprogramming process imparts the ability to transform these cells into different cell types. As a result, iPSCs have the potential to differentiate into various cell types in the body. Induced pluripotent stem cells represent a significant resource for use in regenerative medicine and tissue engineering. These cells could potentially play a valuable role in many medical applications, including the treatment of diseases, tissue repair, and organ transplants.[19]

4. Umbilical cord blood stem cells

Umbilical cord blood stem cells (UCBSCs) are a source of stem cells that have garnered significant attention in the field of medicine in recent years, opening up potential health applications. These special stem cells are obtained from the umbilical cord and placenta of a newborn at the time of birth. Umbilical cord blood stem cells are isolated and processed in the laboratory. This process allows the stem cells to be purified before use. They are of great importance for their potential use in tissue regeneration and therapeutic applications.[20] Umbilical cord blood stem cells, unlike ASCs and ESCs, possess multipotent characteristics. This means they have the ability to be reprogrammed into specific tissues or organs. This feature makes UCBSCs potentially effective in the treatment of various diseases, especially conditions such as blood disorders, immune system disorders, and genetic diseases. Therefore, UCBSCs are increasingly gaining interest in medical research and clinical applications and may play a significant role in addressing more health issues in the future.[21]

5. Amniotic fluid stem cells

Amniotic fluid stem cells (AFSCs) are special stem cells obtained from the amniotic fluid that surrounds the fetus during pregnancy. These stem cells can be obtained from the amniotic sac in the mother's uterus and isolated under laboratory conditions.[22] Amniotic fluid, a natural component of the pregnancy process, is a fluid that assists in the fetus's development within a protective environment. Amniotic fluid stem cells, like other types of stem cells, have significant potential for various health applications and research. These stem cells, especially in fields such as regenerative medicine, tissue engineering, and the treatment of genetic diseases, can be utilized. They possess pluripotent characteristics, meaning they have the capacity to differentiate into many different cell types.[23] Therefore, it is likely that they will play a significant role in addressing health issues in the future. The collection of AFSCs has both ethical and medical advantages, making it an important resource for advances in medical science.[24]

STEM CELL THERAPY FOR RETINAL DISEASES

The mechanisms of action of stem cells occur through various biological processes. Firstly, healthy stem cells contribute to cell replacement by taking the place of degenerated or unhealthy stem cells, aiding in the repair of damaged tissue. Additionally, stem cells provide nutritional support by enhancing the life support of surrounding cells; this is achieved by releasing growth factors. Furthermore, stem cells can regulate the degeneration of retinal cells and blood vessels by demonstrating anti-apoptotic effects.[25] Lastly, stem cells contribute to synapse formation by establishing new synaptic connections. These mechanisms enable stem cells to play a significant role in the treatment of degenerative diseases and tissue repair. Ophthalmology is a medical field that investigates the structure, function, and diseases related to the eyes. This branch of science, which focuses on eye health, encompasses various topics such as the anatomy, physiology, pathology, and treatment methods of the eyes.[26] The eyes are one of the most complex and delicate organs in our body. They hold the key to the quality of human life by determining the ability to see. Therefore, the diagnosis and

treatment of eye health and eye diseases are of utmost importance. In this regard, research in the field of ophthalmology plays a significant role in advancing the diagnosis, treatment, and prevention of eye diseases. Chronic eye diseases such as age-related macular degeneration (MD), cataracts, glaucoma, diabetic retinopathy, and retinitis pigmentosa (RP), especially those causing vision loss, are prominent health issues.[27] These diseases can negatively impact individuals' quality of life and even severely limit functionality. Historically, traces of studies in the field of ophthalmology date back to ancient times. Interest and research in eye diseases and eye health have evolved continuously from Ancient Egypt to Greece, from the Middle Ages to the modern medical era. During this process, significant milestones such as the development of eye surgery, the establishment of optometry, and the invention of glasses for vision correction have been recorded. However, in more recent times, scientific and technological advancements have led to a major transformation in ophthalmology.[28] Advancements in imaging technologies have provided the opportunity to examine the internal structure of the eye in more detail and precision. Minimally invasive procedures such as laser surgery have contributed to making eye surgery safer and more effective. Additionally, research in pharmacotherapy has led to the development of more effective drugs for the treatment of eye diseases. As of 2021, the number and diversity of research conducted in the field of ophthalmology have rapidly increased. These studies encompass a range of important topics, from preventive measures for eye health to early diagnostic strategies, surgical innovations, and genetic-based therapies.[29] In addition, new approaches such as stem cell therapy offer promising potential in the treatment of eye diseases. Diseases in the field of ophthalmology cover a wide range of issues related to the anatomy, physiology, and functions of the eyes. Untreatable retinal diseases often include 'dry-type age-related macular degeneration,' commonly appearing after the age of 50, with no effective treatment for hereditary macular diseases, such as RP and Stargardt disease, commonly known as night blindness. Conditions like Best disease and Leber congenital amaurosis are also mentioned among the untreatable hereditary retinal diseases.[30]

Retinitis pigmentosa

Retinitis pigmentosa is a genetic eye disease that slowly damages the retina, the layer at the back of the eye responsible for detecting light and color. This disease manifests itself with symptoms such as night blindness, tunnel vision, color vision problems, and a narrowing of the visual field. The progression of RP can vary from patient to patient and may lead to vision loss over time. Retinitis pigmentosa results from genetic mutations and can be inherited within families. The age of onset and the severity of the disease can vary depending on these genetic factors.[31] Retinitis pigmentosa currently lacks a definitive treatment; however, ongoing research is exploring new approaches such as stem cell therapy and gene therapy. These treatment methods aim to repair or replace damaged retinal cells. Nevertheless, these approaches are still in the experimental stage, and further scientific investigation is necessary. It is a significant eye disease that can lead to vision loss, and patients should be regularly monitored by a specialized ophthalmologist.[32] Treatment options and management plans are determined based on the specific condition of the patient and aim to improve the quality of life.

Macular degeneration

Macular degeneration is an age-related eye disease that leads to central vision loss. This condition arises from damage to the macula, a specialized region within the retina responsible for clear vision. The macula is crucial for discerning fine details and providing sharp vision. Macular degeneration is classified into two main types: dry and wet.[33]

Dry Macular Degeneration: Dry MD is a condition where cells in the macula gradually undergo damage, and the retinal pigment epithelium (RPE) layer weakens. It typically progresses slowly and can affect central vision. Although there is no definitive treatment yet, certain nutritional supplements (e.g., vitamin A, zinc) may slow down the progression of the disease. Wet Macular Degeneration: Wet MD is a condition characterized by the abnormal growth of blood vessels in the macula. These vessels can leak, leading to vision loss.[34] In the treatment of Wet MD, anti-vascular endothelial growth factor drugs are commonly used. These drugs can help control abnormal blood vessel growth. Macular

degeneration is a leading cause of vision loss in the elderly population. The onset and progression of the disease may be associated with genetic factors, lifestyle, and environmental factors. Early diagnosis is critical in slowing the progression of this disease. Eye doctors diagnose MD through vision tests and retina examinations.[35]

Corneal damage and corneal transplantation

Eye health significantly influences the quality of life for individuals, and the preservation of visual function depends on the overall health of different components of the eye. The cornea is a vital structure that ensures the transparency and focus of the eye. However, corneal damage can occur for various reasons, leading to vision problems. Corneal damage can result from various causes such as trauma, infections, inflammation, and dryness (xerophthalmia).[36] Damage to the cornea impairs vision and prevents the eye from focusing clearly. Such damage can significantly affect patients' daily lives. Coping with corneal damage and restoring visual function may require surgical interventions, such as corneal transplantation. Corneal transplantation is a surgical procedure where a damaged or diseased cornea is replaced with a healthy cornea from a donor.[37] This intervention requires a carefully planned surgical process and can assist the patient in regaining visual quality.

CLINICAL FINDINGS AND FUTURE PERSPECTIVES

The use of stem cells in the treatment of retinal diseases involves various types of stem cells, including ESCs, iPSCs, and MSCs. Embryonic stem cells derived from mouse embryos have the ability to migrate into the retina, displaying neural markers, and can enhance photoreceptor viability in degenerated retina models. Similarly, in rats, the integration of neural cells derived from ESCs into the retina has been observed to be effective, demonstrating neuroprotective effects.[38] Transplants of RPE cells derived from ESCs have yielded highly successful outcomes. Experiments conducted on the MERTK gene-deficient retinal degeneration model in mice have shown improvement in photoreceptor functions and increased visual performance. Initial clinical studies in humans, initiated with FDA approval, involved the subretinal application of MA09-hRPE (human ESC-derived RPE) cells in cases of dry-type age-related MD and Stargardt macular dystrophy, demonstrating visual improvement and increased quality of life without observed adverse effects.[39] These significant findings emphasize the potential of stem cell-based therapies in the treatment of degenerative retinal diseases. In the future, further clinical studies, planned to include different groups of retinal diseases and treatment methods, will continue to unfold with the aim of achieving promising results.

Importance and risks of iPSCs applications

Induced pluripotent stem cells are obtained by reprogramming adult somatic fibroblast cells through various methods under laboratory conditions. These cells possess versatile potential similar to ESCs but have some differences. They are less sensitive to immune reactions due to their autologous nature (patient's own cells), and therefore, they require lower immunosuppression requirements.[40] However, it should be noted that abnormal genetic changes may occur in some iPSCs, potentially triggering T-cell-based immune responses. Due to the multiple passages that cells undergo during iPSC and ESC production, there can be certain risks. Changes such as the activation of oncogenes and suppression of tumor suppressor genes may occur during this process, increasing the risk of tumor formation. Tumor formation is believed to originate from undifferentiated iPSCs. Preclinical studies have generally observed tumor formation within the first 3-6 months.[41] Therefore, the use of iPSCs entails both significant advantages and potential risks. Careful assessment of these risks plays a critical role in the development of iPSC-based therapies. Studies evaluating iPSC usage in rats have observed improvement in retinal functions measured by electroretinogram (ERG). One such study demonstrated the conversion of human iPSCs into RPE cells in rats, enhancing retinal functions. These cells exhibited RPE markers and improved ERG responses compared to the control group.[42] These results demonstrate that iPSCs can function both morphologically and functionally and are safe. These encouraging findings have served as inspiration for clinical trials in humans. In Japan, a study has been initiated using iPSCs derived from the patient's own epithelial cells.

In this study, the patient's epithelial cells were transformed into RPE cells under laboratory conditions and then transplanted subretinally back into the same patient. However, this study was conducted in only one patient and was halted before applying to a second patient in March 2015. There are two reasons for this situation.[43] Firstly, new regenerative medicine laws in Japan have hindered the continuation of the study. Secondly, a genetic mutation was detected in the induced cells of the planned second patient, which was not present in the original cells. It was presumed that these mutations originated from the induction and reprogramming processes.[44]

The process of stem cell therapy for eye diseases

Various examinations are necessary for the evaluation of patients eligible for stem cell therapy for eye diseases. These examinations include the assessment of visual fields, optical coherence tomography (OCT), and electrophysiological tests. These tests are utilized to determine whether an individual is suitable for stem cell therapy. For ideal candidates, approval from the Stem Cell Advisory Board within the Ministry of Health must be obtained before the application of stem cell therapy.[45] This board assesses the eligibility of patients for treatment. Mesenchymal stem cells are used for stem cell therapy. In terms of application, the suprachoroidal route (outside layer of the eye) is preferred due to its safety and non-interference with other treatments. The surgical procedure can be performed under general or local anesthesia depending on the patient's preference.[46] Surgery can be performed on a single eye or both eyes during the same session. Following the surgical intervention, the patient undergoes eye drop therapy for one month. Check-ups are conducted on the first, third, and sixth months after the surgical procedure. Subsequent follow-ups, which occur every six months, involve visual field and OCT tests.[47]

In conclusion, early diagnosis is considered to enhance the success of ophthalmologic stem cell therapy. However, it can be stated that specific criteria must be met for the application of this treatment. Firstly, the eye structure must be intact for stem cell therapy to be applicable. It is known that stem cell therapy is not effective in patients with structural problems in the eye, such as severe deformities or shrinkage. The second crucial factor is the severity of visual impairment. Patients with no visual abilities do not benefit from stem cell applications. Therefore, the ideal patient group for stem cell therapy consists of individuals without advanced vision loss. Hence, the primary goal of stem cell therapy is to halt the progression of the disease. Positive outcomes, such as visual improvement and expanded visual fields, are achieved in approximately 60 to 80% of treated patients. The initial level of vision before surgical intervention is considered an indicator of visual recovery after treatment. Additionally, an expansion of the visual field and improved retinal functions have been observed post-treatment. The earlier the treatment is applied, the more favorable the results obtained. Therefore, early diagnosis and treatment play a crucial role in the management of eye diseases through stem cell therapy. Stem cell applications, particularly based on the results of Phase I/II studies, have been progressing quite successfully. No significant concern regarding systemic side effects has been observed in these studies. Serious ocular side effects such as tumor formation or uncontrolled cell proliferation have not been reported. These results demonstrate the reliability of stem cell-based treatments and their potential contributions to eye health. Improvements recorded, especially in visual functions, have been a source of great encouragement for researchers and patients in this field. However, risks that could lead to vision loss, such as vitreoretinal complications following intravitreal and subretinal applications, should not be overlooked. Therefore, caution and experience are necessary in the implementation of these treatments. Nevertheless, to better understand the future role of stem cell-based therapies, further research involving a broader patient group and relying on longer-term follow-up results is required. Currently, numerous studies on the use of stem cells for the treatment of various retinal diseases are ongoing, and the results of these studies are eagerly anticipated with great interest and hope. Advances in this field could be a significant turning point in the treatment of blindness in the future.

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