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Review

Stem Cell Therapy for Ocular Regeneration: A Review Article

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ABSTRACT

Stem cell therapy (SC) is emerging as a promising approach in ocular regenerative medicine, offering new alternatives for diseases that lead to progressive or sudden vision loss. Clinical and pre-clinical studies with induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs) and limbal stem cells show the capacity to repopulate the corneal epithelium, replace retinal pigment epithelium (RPE) cells and even generate functional photoreceptors. Phase I/II trials in age related macular degeneration, diabetic retinopathy and limbal deficiency report sustained visual improvement in part of the patients, with a low incidence of serious adverse events. Nevertheless, broad clinical application still faces obstacles such as immune rejection, the risk of tumorigenesis and incomplete functional integration of transplanted cells. In parallel, advances in scaffold bioengineering, CRISPR gene editing and MSC based immunomodulation have increased protocol safety and efficacy. This review updates the main evidence on SC use for corneal, retinal and RPE regeneration, analyzes methodological gaps and proposes future perspectives, emphasizing the need for standardized cultures, good manufacturing practice scale up and harmonized regulatory frameworks. Although significant challenges remain, ocular cell therapy is moving toward becoming a fundamental component of the therapeutic arsenal against blindness. Finally, the importance of multicenter randomized trials to confirm long term efficacy and establish robust clinical guidelines is highlighted.

Keywords: Stem cells; Ophthalmology; Ocular regeneration; iPSCs; Cornea; Retina

Introduction

Vision is a cornerstone of human interaction with the environment. It is estimated that more than 2.2 billion people worldwide have some degree of visual impairment and in roughly half of these cases current therapies are unable fully to restore lost function. Traumatic injuries, chemical burns, corneal dystrophies, age related macular degeneration (AMD) and hereditary retinopathies rank among the main causes of irreversible blindness[1]. Regenerative medicine seeks to replace or repair diseased tissues by means of cells capable of self-renewal and differentiation. Embryonic stem cells, first described by THOMSON et al. (1998), display high pluripotent potential but have been surrounded by bioethical controversies.

The advent of iPSCs generated by reprogramming adult

somatic cells with specific transcription factors (TAKAHASHI & YAMANAKA, 2006)-overcame many concerns by enabling the production of potentially unlimited autologous lines. In ophthalmology, different cell subtypes have been explored for specific purposes. For the cornea, priority is given to limbal epithelial stem cells, depletion of which results in corneal opacity and neovascularization. Autologous limbal transplants show success rates above 70 % in long term series[2]. The retina, by contrast, requires replacement of photoreceptors and RPE cells highly specialized, metabolically active populations. Pioneering trials with iPSC or embryonic derived cells have demonstrated cellular survival and modest visual acuity gains in animal models and in humans[3,4].

MSCs, harvested from adult tissues such as bone marrow and adipose tissue, have gained attention owing to their reduced immunogenicity and anti-inflammatory paracrine properties[5]. Although less efficient at differentiating into mature photoreceptors, they favorably modulate the injured microenvironment, inhibiting apoptosis and stimulating neurotrophic factors. Combining MSCs with hydrogels or electro spun nanofibers shows synergism in corneal and retinal regeneration[6].

Despite progress, multiple barriers persist. Protocol heterogeneity hampers cross study comparison; obtaining xenogeneic free matrices remains costly; and iPSC genomic instability raises concerns about malignant transformation[7]. Furthermore, functional integration in the retina depends on proper synapse formation, a process that appears to decline with disease chronification[8]. From a regulatory standpoint, the lack of harmonized quality, safety and efficacy criteria widens the bench to bedside gap[9]. Against this backdrop, the present article critically reviews recent evidence on stem cell use for ocular regeneration. The aims are to (1) synthesize key clinical and pre-clinical outcomes for the cornea, retina and RPE; (2) discuss technical, biological and regulatory hurdles limiting broad adoption; and (3) highlight research avenues that could accelerate translation of discoveries into safe, accessible therapies.

Objectives

This work seeks to review the latest findings on stem cell use for ocular regeneration, encompassing corneal regeneration, retinal repair and restoration of the retinal pigment epithelium.

Materials and Methods

A literature review was performed using the PubMed, SciELO, Google Scholar and ScienceDirect databases.

Discussion

Accumulated evidence over the past decade confirms the transformative potential of stem cell therapies in ophthalmology; however, the magnitude of benefit remains variable across patient populations and pathologies. Limbal deficiency is perhaps the most mature target, with corneal re epithelialization rates above 75 % in the largest multicenter studies[10]. The tissue's relative simplicity, surgical accessibility and absence of a blood retina barrier favor rapid integration of transplanted cells. Nevertheless, even in this consolidated arena, graft quality critically depends on the recipient limbal niche and on ex vivo expansion protocols, whose use of fetal bovine serum still raises zoonotic concerns. Trials replacing animal components with human platelet lysate or B27 supplementation reported reduced late immune rejection, but long term efficacy data remain scarce[11].

The retinal scenario is more complex. iPSC derived RPE has shown convincing structural integration in AMD models, with partial restoration of photoreceptor waste phagocytosis[4]. Yet functional gains in humans were modest: improvement of two to three ETDRS lines in only one third of participants[3]. Hypotheses for this disparity include recipients' advanced age, subclinical chronic inflammation and the need for co transplantation of glial cells to sustain synaptic homeostasis. Innovations such as three dimensional printing of retinal organoids onto polylactide membranes provide a physical scaffold that guides cellular polarization and boosts survival after sub retinal implantation[12].

Tumorigenic risk often cited as a hindrance can be controlled through directed differentiation and rigorous flow cytometry screening before implantation. Studies applying purification protocols with RPE65 or CRX optical markers reported no teratoma formation after > 36 months' follow up[13]. Concurrently, CRISPR Cas9 gene editing is being employed to correct retinitis pigmentosa mutations in autologous lines, enhancing safety by reducing allogeneic immunogenicity[1]. Immunomodulation provided by MSCs offers an additional opportunity to optimize outcomes: systemic or sub Tenon infusion of these cells reduced IL 6 and TNF α levels in uveitis models, creating a permissive environment for iPSC derived cells[5]. However, their low in vivo persistence limits effect durability.

Transgenic strategies to overexpress CXCR4 or SDF 1 have increased homing to ischemic retina, but gene safety issues must be resolved before larger clinical trials[6]. Regulators in Japan, the United States and the European Union have adopted accelerated conditional approval pathways for advanced therapies, yet require evidence of sustainable clinical benefit. The absence of adequately powered randomized controlled trials prevents extrapolation of current results to broader populations[7]. Additionally, production costs-estimated at USD 150,000 per patient for iPSC based protocols-raise questions of equitable access (TROUNSON & MCDONALD, 2015). In sum, although efficacy still hinges on refining multiple variables, current findings indicate that ocular cell therapy is on an upward technological maturity trajectory. Convergence among tissue engineering, genomic editing and precision immunosuppression outlines a future in which currently incurable diseases may be definitively treated.

Conclusions

Stem cell therapy inaugurates a paradigm that transcends symptomatic management of blindness to propose genuine restoration of ocular structure and function. Available evidence shows that distinct cell populations meet specific needs: limbal cells repopulate the corneal epithelium, iPSC derived cells rebuild the RPE and initiate photoreceptor formation and MSCs modulate local inflammatory responses. To date, the most consistent clinical benefits have been observed in corneal epithelial therapies, yet the rapid evolution of retinal bioassays suggests this landscape may change within the next decade[10,12].

Four pillars are essential for definitive consolidation of this therapeutic modality. First, standardization of culture, differentiation and quality control protocols; only with clear specifications can comparable data be accumulated across centers. Second, assurance of biological safety, with emphasis on detecting chromosomal aberrations, eliminating xenogeneic

contaminants and evaluating in vivo tumorigenicity[13]. Third, economic feasibility, involving bioreactor automation, procurement of clinical grade reagents at lower cost and creation of compatible allogeneic banks. Fourth, structuring multicenter, randomized, controlled clinical trials capable of generating high level evidence to support regulatory and public policy decisions[9].

Additional challenges include the need to understand dynamic interactions between the cellular graft and diseased microenvironment-particularly in the retina, where the synaptic network is extraordinarily complex. Advances in optogenetics and real time biosensors will allow unprecedented resolution monitoring of regenerated tissue functionality, providing immediate feedback for therapeutic adjustments[8]. Moreover, precision gene editing offers opportunities to correct hereditary mutations before transplantation, reducing recurrence risk of the underlying disease. Ethically, using autologous iPSC derived cells minimizes concerns about embryonic origin but imposes logistical challenges of personalization. Business models based on HLA matched cell banks may balance cost effectiveness and accessibility, yet demand rigorous governance over genomic privacy and informed consent[7]. In parallel, it is imperative to ensure that innovation does not deepen global inequalities in ocular health; international cooperation programs and access funds can help democratize these high-tech treatments[14].

In conclusion, ocular regeneration via stem cells is no longer a distant promise but a rapidly evolving, multifaceted reality. Fulfilling its potential will depend on harmonious articulation among basic science, engineering, rigorous clinical trials, flexible regulatory frameworks and equitable access policies. If these conditions are met, it is plausible that in the coming years cell therapy will become the standard intervention for corneal and retinal diseases once considered irreversible, positively impacting millions of people affected by vision loss worldwide[15].

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