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Posted Date: 5 February 2025

doi: 10.20944/preprints202502.0327.v1

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Review

Advances in Cell-Based or Cell-Biomaterial Scaffolds for the Treatment of Age-Related Macular Degeneration

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Abstract: Age-related macular degeneration (AMD) is a degenerative retina disease characterized by irreversible damage to macular cells and has become one of the leading causes of blindness in the elderly worldwide. Therapies based on cells or cell-biomaterial scaffolds are popular AMD treatments in recent years, where cell therapy is the use of cell types such as progenitor/stem cells, which are delivered into the subretinal space by injection or vector transplantation to treat AMD. Meanwhile, cell-biomaterial scaffolds delivered to the lesion site by vector transplantation have been widely developed, and the implanted cell-biomaterial scaffolds implanted cell-biomaterial scaffolds can promote the reintegration of cells at the lesion site and solve the problems of translocation and discrete cellular structure produced by cell injection. Although these methods have achieved some results, a large number of preclinical studies and clinical trials are still needed to verify their stability and reliability. Therefore, this article provides a review of the latest findings and real-life challenges of cell-based and cell-biomaterial scaffolds for the treatment of AMD to offer new ideas for subsequent disease prevention and treatment of AMD.

Keywords: age-related macular degeneration; retinal pigment epithelium; stem cells; tissue engineering

1. Introduction

Retinal Degenerative Diseases include hereditary, induced, acquired, and other forms of characteristics, and are the leading cause of blindness in the global population [1]. The main cause of retinal degenerative diseases is the loss of photoreceptors, impaired function, or apoptosis of nerve cells, once the photoreceptors are damaged, the rest of the retinal cells are successively damaged and the regeneration of the retina is very weak, which ultimately leads to irreversible blindness[2].In this article, we will focus on a typical type of retinal degenerative disease: age-related macular degeneration (AMD).

AMD is one of the most common retinal degenerative diseases, there are two forms of AMD, dry AMD and wet AMD, which is caused by the damage and degeneration of photoreceptors and retinal pigment epithelium (RPE) cells in the retina [2]. The number of AMD patients worldwide is expected to reach 288 million by 2040 [3], which predicts that AMD may cause major public health problems such as impaired population health, increased economic stress on patients, and increased socio-economic burden. Some current work has been done to rescue and slow down the progression of the disease by injecting drugs into the vitreous (long-acting formulations, extended-release formulations, topical formulations, combinations of formulations, and gene therapy formulations), or by using neuroprotective biomolecules [4–6], but unfortunately there are few effective ways to treat AMD at this time, as drugs can only treat, but not replace, the lost retinal cells.

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Cell therapy is widely recognized as the most clinically promising treatment due to its unique clinical applications and therapeutic advantages. Fisher et al. demonstrated that RPE dysfunction and degeneration precede photoreceptor damage in AMD [7], and that impaired function of RPE cells is a key early contributor to clinically relevant AMD [8], meanwhile, RPE replacement therapy has been a fast and promising treatment for AMD [9]. Therefore, researchers have extensively explored the use of progenitor/stem cell-derived RPE for AMD salvage, but there are also limitations to the therapeutic efficacy and therapeutic efficiency of cell therapy by cell proliferation, differentiation, in vivo survival, migration, and integration [10]. Delivered cell-biomaterial scaffolds have also been proposed to promote cell survival and differentiation [11]. The basic concept of cell-biomaterial scaffolds is to select suitable biomaterials to make scaffolds that support the growth of cells on them, subsequently grow cells on them in culture to make them functional monolayers, and finally transplant them under the diseased parts of the retina to treat AMD. The materials used to make cell-biomaterial scaffolds need to be able to mimic the in vivo microenvironment, be biocompatible, and have suitable mechanical properties [12]. This review will review studies from the past few years that have revealed substantial progress in the treatment of AMD with cellular and cellular-biomaterial scaffolds, discussing the real-life challenges and future perspectives of alternative therapies to RPE.

2. Age-Related Macular Degeneration

The retina is a layered light-sensitive tissue arranged at the back of the eye and is approximately 0.5 mm thick [13]. The RPE is located near the neural retina and is a highly specialized layer of polarized epithelial cells involved in the recycling of visual pigments and the maintenance of the structural and functional integrity and health of the photoreceptors[14].AMD results from irreversible damage to the RPE and photoreceptor cells in the retina permanent vision loss and is the leading cause of blindness in the elderly population[15].AMD is classified into two forms, dry (also known as atrophic or non-exudative) and wet (also known as neovascular or exudative), with dry AMD being the more common form, characterized by vitreous warts and geographic atrophy (GA) extending into the central concavity[16], this atrophy results from degenerative changes in the RPE cells, and when the atrophy involves the central visual acuity, the eye presents with advanced non-exudative AMD and irreversible vision loss[17]. Dry AMD evolves into wet AMD as the disease progresses, which is closely related to the absence of choroidal neovascularization (CNV), hypoxia, and subsequent neovascularization [18]. Dry AMD evolves into wet AMD as the disease progresses, which is closely related to the absence of CNV, hypoxia, and subsequent neovascularization [16,19].

3. Treatment of AMD

AMD occurs as a result of a multifactorial (genetic, environmental, metabolic, and functional) combination of factors, and the pathogenesis is complex and the underlying pathology is not well understood[20]. Currently, the main treatments for AMD include antibodies, genes, and cells. Antibody-based anti-VEGF therapy has completely transformed the treatment of wet AMD, which is currently the majority of clinical treatments[15]. In contrast, the therapeutic target of wet AMD in gene therapy is primarily VEGF, and the need for regular intravitreal injections of anti-VEGF antibodies may be reduced by intravitreous delivery of VEGF antagonists. Although antibody studies and genetic studies targeting inhibition of the complement pathway are ongoing, there are no effective treatments for early or advanced dry AMD[21]. As mentioned earlier, RPE replacement is currently the most promising treatment approach, therefore, the subsequent focus will be on RPE replacement therapies based on cellular and cellular-biomaterial scaffolds. Table 1 summarizes recent advances in the three aforementioned therapeutic approaches.

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Table 1. Main treatments for dry and wet AMD.

Treatment	AMD Classification	
	Dry AMD	Wet AMD
Antibody	Lampalizumab[22] Ecuccab[24] HtrA serine peptidase 1 antibody[26]	Ranibizumab[23] Bevacizumab[25] Aflibercept[27]
Gene	C3 complement inhibitor Pegcetacoplan（APL-2）[28] GT005[32] AAVCAGsCD59[21] Recombinant human complement factor (GEM103)[35]	Faricimab[29] Brolucizumab[30] Bispecific antibodies[31] HMR59[33] ABBV-RGX-314[34] ADVM-022[36]
Cell	Human embryonic stem cell (hESC)-derived RPE[37] Human umbilical cord tissue-derived cells (palucorcel)[39] Encapsulated Cell Technology (ECT)[41] Bone marrow-derived stem cells (BMSC)[43]	Coated synthetic basement membrane loaded with human ESC-derived RPE patches[38] PDMS membrane coated with laminin and liposomes loaded with dexamethasone[40] Human ESC Derived RPE[42]

3.1. Cellular Therapy

Cellular therapy is one of the most promising therapies for the treatment of degenerative retinal diseases such as AMD, aiming at cell replacement and neuroprotection. Neuroprotective therapies can protect cells before apoptosis, but in patients who are in the later stages of the disease, neuroprotection is lost as they have already lost their vision. There is evidence that the main feature of AMD is damage to the RPE and photoreceptors leading to loss of central vision[44], and repair and replacement of the damaged RPE has been investigated to some extent. Rajendran et al. treated

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AMD by injecting autologous RPE cell suspensions, but there were also problems with inflammation at the site of the injection and only short-term effects could be observed[45], and autologous transplants are prone to carry the same genes that cause disease manifestations in AMD[46]. Chae et al. found that eliminating senescent cells is a potential new therapeutic approach to treating AMD and that eliminating senescent cells to allow healthy cells to be the therapeutic target may be more effective than using senescent cells as a therapeutic target for AMD[47].

Although early cellular therapies were effective in the treatment of AMD, their various shortcomings can create new health risks for patients and the RPE lacks the ability to self-repair and renew [10], so many researchers have attempted to transform progenitor/stem cells with differentiation properties into healthy RPE, which can be transplanted in order to regenerate the damaged RPE.

Stem cells are currently a popular research area in the research community and hold great promise in the field of regenerative medicine, and therefore could be a potential method for restoring vision in AMD patients[48,49]. Stem cells are usually defined as undifferentiated cells and are mainly characterized by their ability to self-renew, proliferate into an undifferentiated state of homogeneous pluripotent stem cells, and differentiate into different cell types[50,51]. Table 2 summarizes several major cell sources for the treatment of AMD and their respective advantages and disadvantages, including retinal progenitor cells (RPCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs). Coco-Martin et al. suggest that these cells are a potential source of retinal cell transplants, which can be developed into RPEs for clinical applications, photoreceptors, or ganglion cells[2]. A brief overview of these cells is provided below.

Table 2. Main cell sources used for the treatment of AMD.

Cell type	Vantage	Challenge	Quote
RPCs	Exhibits specific stem cell proliferation and differentiation properties; can differentiate into a variety of retinal cell types; avoids ethical issues; lowers the risk of immune rejection and tumor development	Limited proliferative capacity; lack of sufficient donor cells; limited ability to differentiate into specific target cells	[52]
ESCs	Potential to differentiate into various types of cells	Ethical issues; risk of tumorigenesis; risk of immune rejection	[53]
iPSCs	Reprogrammed from adult somatic cells to avoid ethical issues Potential to differentiate into various types of cells	Tumorigenic risk; Genetic or epigenetic abnormalities caused by reprogramming;	[54]
MSCs	Derived from adult tissues, simple and widely available, immunomodulatory, low tumourigenicity	Low survival rate due to microenvironmental effects at the site of injury; further work is needed to determine the best source of donors	[55]

3.1.1. RPC

RPC has the ability to avoid tumourigenesis and immunosuppression, therefore, RPE or photoreceptors derived from RPC differentiation are considered to be a suitable and promising transplantation resource[56–58]. However, the survival of transplanted RPC and the low number of in vitro expansions limit its clinical application, and novel cell culture and cell delivery techniques need to be applied to overcome the limitations of RPC[59].

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3.1.2. ESC

As pluripotent stem cells, ESC are pluripotent, capable of self-renewal, and have the potential to differentiate into a variety of cell types[60]. Hall et al. have found that ESC can differentiate into specific cell types[61]. Klimanskaya et al. claimed that ESC were the first pluripotent stem cells to be used in the production of RPE[62], and Limnios et al. and Garcia et al. suggested that human ESC can successfully produce human RPE[63,64]. Thus, ESC has great potential for differentiation into retinal cells, nevertheless, there are ethical issues, immune rejection, and risk of tumourigenesis[65].

3.1.3. iPSC

iPSC also belongs to pluripotent stem cells, which have the ability of unlimited renewal and differentiation into a variety of cells[66] .iPSCs are derived from somatic cells and reprogrammed by introducing specific transcription factors[17]. Theoretically, since iPSC can be extracted from any adult tissue without immune rejection, research on iPSC has been progressively more fervent than that on ESC in recent years. Among the iPSC therapies for retinal diseases, a recent study by Akiba et al. has shown that human iPSC can be transformed into RPE cells[67]. In addition, D'Antonio-Chronowska et al. used small molecule-derived human RPE cells under serum-free conditions, a cost-effective and highly reproducible method for the simple and robust production of hundreds of human RPE cells for high-throughput applications[68]. Truong et al. investigated a platform for the automated production of human iPSCs and the facilitation of their differentiation into retinal A platform for automated production of human iPSCs and promotion of their differentiation into retinal pigment epithelial cells is expected to enable mass production of RPE in the future, enabling the repair of vision damage in AMD patients[69].

3.1.4. MSC

MSCs are an excellent source of stem cells and avoid ethical issues similar to ESC due to their ability to be isolated in large quantities from perinatal derivatives (umbilical cord, amniotic membrane) or adult tissues (bone marrow, fat, brain, heart, teeth, gut)[70]. The main types of MSC targeted for retinal diseases are MSC from bone marrow and MSC from umbilical cord. MSC from bone marrow was first isolated and extracted by Friedenstein et al.[71], however, it suffers from low survival and low level of expression when differentiated into RPE for implantation in vivo, so Huang et al. improved these problems by introducing the soluble cytokine ciliary neurotrophic factor. Trophic factor to ameliorate these problems, which can activate phagocytosis of photoreceptor cells and RPE, promote retinal healing, and help MSC differentiate into RPE, which is a welcome advancement in the field of retinal regeneration[72].

In addition, MSC derived from donor umbilical cords are being explored for the treatment of retinal diseases. Umbilical cord-derived MSC does not have invasive acquisition behavior compared to bone marrow-derived MSC, it is easy to access, has better proliferation and differentiation ability, and lower risk of immune rejection[70]. Zhu et al. induced MSC extracted from human umbilical cord tissues into RPE cells, which made it a potent candidate cell for the treatment of AMD[73]. In summary, MSC has great potential in the field of retinal cell regeneration for the future treatment of AMD.

3.2. Cell-Biomaterial Scaffold Therapy

As described in previous studies, cell adhesion, growth, migration, and differentiation are dependent on the nature of the cell-biomaterial scaffold. However, the properties of the scaffolds are influenced by mechanical properties, surface morphology, and bioactivity. Delivery of cell-biomaterial scaffolds to the subretinal space requires surgery, resulting in some invasiveness, and the efficacy and mechanism of cell replacement remain unproven in patients with less severe disease who refuse treatment because of concerns that surgery carries the risk of aggravating visual

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impairment, and in patients with severe visual impairment who no longer have an ocular environment in which to interact with the replacement scaffold[11].

3.2.1. Cell-Biomaterial Scaffold Functionality

Although cell therapy holds great promise for the treatment of AMD disease, cell adhesion, distribution, long-term survival, and proper functioning at the transplant site without any infection[74] remain major challenges. Gullapalli et al. found that cell suspensions need to adhere to the scaffolds within 24 hrs of injection or apoptosis occurs and the suspensions were prone to dislocation, compared to the higher survival rate of cells replaced using cell-biomaterial scaffolds[75]. The reason for this is that cell-biomaterial scaffolds provide physical support as a carrier in cell delivery, survival, and integration. In addition, cell-biomaterial scaffolds as a vehicle for cell delivery need to be biodegradable, non-toxic, thin, robust and conform to the curvature of the retina.

3.2.2. Cells - Biomaterial Scaffold Properties

Biomaterials based on natural and synthetic polymers are now widely used as delivery scaffolds for various types of retinal cells[12]. Natural polymers are widely used due to their good bioactivity, low immunogenicity, excellent cytocompatibility, and ability to mimic the role of natural tissues. However, their possible risk of immune rejection after implantation, inflammatory reactions, and poor mechanical properties are currently the main limiting factors for their application[76]. Therefore, the physicochemical properties are usually altered by controlling the molecular composition of the polymer to suit the actual range of use. To satisfy the properties as scaffolds, it is possible to adapt the resulting cell-biomaterial scaffolds to the conditions of practical application by chemically modifying the natural polymers[77], making blends with synthetic polymers[78], cross-linking[79] and physically modifying[80]. Although synthetic polymers possess excellent mechanical properties, biodegradability, and three-dimensional structure, they have obvious drawbacks, such as poor cell attachment due to lack of bioactivity. Still, they can be chemically modified[81], physically surface modified[82], biologically modified[83], polymer blended (blending of two synthetic polymers or more or natural and synthetic polymers)[84,85], and mineralization [86]were used to improve their properties. Table 3 summarizes the common biological and synthetic polymers used in making cell-biomaterial scaffolds.

Table 3. Biological and synthetic polymers for making cell-biomaterial scaffolds.

Polymers	Vantage	Drawbacks	Quote
Gelatine	Biocompatibility, biodegradability, non-toxicity, plasticity and adhesion	High moisture absorption and poor mechanical properties	[87–89]
Chitosan	Low cost, antimicrobial, low toxicity, biodegradable and biocompatible	Low solubility at physiological pH, easy interaction with other biological structures	[88,90–93]
Collagen	Biocompatibility, Biomimetic, Biodegradability and Haemostasis	Poor mechanical properties, poor thermal properties, enzymatic degradation	[94–97]
Alginate	Easily extracted, abundantly available, biocompatible, biodegradable and non-toxic	high cost	[89,98–100]

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Hyaluronic Acid	Antibacterial, antioxidant, biodegradable	Readily degradable, potentially variable elements	[88,101–104]
Poly (lactic-co-glycolic acid) (PLGA)	Good mechanical properties, non-toxic, biodegradable, non-immunogenic, controlled drug release	/	[105–109]
Polycaprolactone (PCL)	Biocompatible, Low cost, absorbable	Insufficient mechanical strength, low number of cellular recognition sites, poor bioactivity, hydrophobicity	[95,110,111]
Polylactic Acid (PLA)	Biocompatibility, biodegradability, piezoelectricity	Poor mechanical properties, hydrophobicity, poor electrical conductivity	[112,113]
Parylene-C	Mechanical flexibility, optical transparency, low inherent stresses	Low air permeability, low mechanical strength, limited thermal budget	[114–117]

4. Key Challenges of RPE Alternative Therapies

The main challenges for the clinical application of cell therapies in AMD patients are (1) the survival of cells used for RPE transplantation[50]and the determination of the long-term tissue replacement capacity after integration of the choroid[118]; (2) the risk of immune rejection after cell transplantation[119]; (3) the establishment of a safe and efficient cell-biomaterial scaffolding model based on stem cells to be delivered to the retinal interstitial space[120], and (4) development of evaluation methods to monitor RPE replacement therapy[11].

4.1. Cell Graft Survival and Long-Term Replacement Capability

One of the difficulties in cell replacement therapy is cell survival after cell replacement, as mentioned earlier, using stem cells as a donor source has the advantage of continuous self-renewal and differentiation into various cell types[121]. However, the healthy and stable transformation of cells from stem cells into RPE for transplantation into patients and long-term survival of RPE is a challenging issue, for example, the grafts enter the patient and undergo apoptosis due to inflammatory response, failure of choroidal integration, etc. Alhasani et al. inhibited RPE cell survival by adding molecules that improve RPE survival, such as taurine deoxycholic acid, which inhibits oxidative damage, inflammation, and endoplasmic reticulum stress, leading to RPE protection[122].

4.2. Host Tissue Rejection

The current safety concerns that have arisen with stem cell-based therapies focus on the proliferation of cells, the occurrence of ectopic tissues, and the tumorigenicity of the injected cell mass. This issue has not arisen in clinical studies of autologous iPSC, but this concern would be present with allogeneic transplants and preclinical trials are still required to test and improve[123].

4.3. Cell Delivery

Biomaterial scaffolds that support cell growth, manufactured using tissue engineering methods, are a common option for RPE replacement therapy. Cell-biomaterial scaffolds can overcome the challenges of traditional cell delivery, such as integration, weak cell adhesion low viability, and functional polarization, but they also suffer from poor mechanical properties and biocompatibility. Therefore, further improvements are needed to apply cell-biomaterial scaffolds to RPE alternative

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therapies, and new tissue-engineering protocols need to be developed to increase RPE survival, improve RPE survival, adhesion, integration, and greatly improve apoptosis of transplanted cells in the host tissue environment[124].

4.4. Evaluation of Cell Replacement Therapies

After intervention with stem cell-based cell therapies, even successful follow-up of RPE transplantation may be limited, e.g., successful adherence, distribution, and long-term survival of transplanted cells at the transplantation site, and normal functioning of the cells[74]. Therefore, follow-up evaluation of the function of transplanted cells is important. Strategies to monitor RPE adaptation and integration at the cellular level should be developed that are capable of accurately quantifying the amount of RPE and assessing its functional distribution in the retina. Develop reliable methods to examine and characterize the improvement in AMD after RPE replacement therapy.

4.5. Organoids

Organoids are emerging as promising biological solutions for regenerative retinas as a technology that can mimic natural organs[125]. Organoids, as the name suggests, can be developed into a variety of organ structures, and because they are close to real organs in morphology, tissue structure, and functional operation, organoids have a promising future in basic medical research, drug screening, disease modeling, regenerative medicine transplantation, and gene therapy[126].

Based on this, the development of retinal organoids has equally great potential. It has been shown that both ESCs and iPSCs have the ability to differentiate into 3D retinal organoids[17,127]. As mentioned earlier, RPE injury is an early event in AMD[8], which is associated with apoptosis of photoreceptors and other retinal cells[128], and the development of retinal organoids is able to compensate for the loss of retinal cells that occurs as a result. Therefore, in the future, retinal organoids will become one of the important avenues as regenerative tissues for the treatment of retinal degenerative diseases through cell transplantation. To provide a canonical system for the study of human photoreceptors, Cuevas et al. genetically edited NRL-deficient embryonic stem cell lines into retinal organoids[129]; Matsuyama et al. restored light responsiveness by introducing genetically engineered mouse iPSC/ESC-derived retinal patches to establish synaptic connections with the host[130]. Lin et al. also explored the potential for means of ameliorating RPE dysfunction through retinal organoid transplantation[131]. Overall, the development of retinal organoids does hold great promise. However, retinal organoids still face many difficulties, and suitable solutions need to be further developed to solve the problems of mass production, safety, and efficacy that have yet to be verified.

5. Conclusions

AMD is a common retinal degenerative disease and is one of the leading causes of blindness in the elderly worldwide. Damage to the RPE is a key factor leading to early AMD. However, current treatments are limited in that they can only delay the progression of the disease and cannot cure permanent visual impairment. Cell-based, gene-based, and antibody-based therapies are all being trialed in the clinic, and current results suggest that these modalities have potential and need to be further explored. Recent research suggests that replacing damaged RPE is a very promising treatment, and cell-based or cell-biomaterial scaffold therapies could present a solution to this problem, but there are some major challenges associated with both of these approaches.

To date, the main challenges of cell-based or cell-biomaterial scaffold therapies include poor cell graft survival and integration, insufficient long-term replacement capacity, host rejection, difficulties in cell delivery, control of stem cell tumourigenicity, and development of systems for monitoring and evaluating cell regeneration after regeneration. Among these cell delivery, survival, and integration issues can be addressed by developing suitable tissue-engineered cells -biomaterial scaffolds and producing visual organoids. However, the tissue-engineered cell-biomaterial scaffolds also include

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the problems of post-implantation inflammatory response and whether the degradation time can support the survival time of RPE, while the organoids face the problems of safety, high efficiency, and mass production, and they all need to be supported by suitable protocols and complete technological methods to derive RPE cells with functionality, to fully achieve the purpose of restoring visual function.

Authors' contributions: Ziming Li participated in the conception and writing of the article, while Zhiyong Hu and Zhixian Gao provided guidance and editing for the article. All authors read and approved the final manuscript.

Funding: The funding support for this article comes from the National Key Research and Development Program 2022YFF1202901.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Acknowledgments: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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