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The application of regenerative medicine in ophthalmology

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The causes of blindness vary widely around the world including the degeneration of particular groups of retinal cells, such as retinal pigment epithelium (RPE), photoreceptors, and retinal ganglion cells. These cells could be generated ex vivo from progenitor stem cells thanks to advancements in retinal regenerative medicine over the past ten years. Here, we discuss the development of cell replacement using novel technologies, to restore eyesight in degenerative diseases. We go over the state of advanced preclinical research for other cell kinds as well as human clinical trials for RPE transplantation. We also discuss the developments in using endogenous progenitor cells to fix retinal degeneration in situ. Last but not least, we give a high-level summary of the development of prosthetic ocular vision restoration using advanced photovoltaic devices, opsin-based gene therapy, and small-molecule photoswitches.

Keywords: *Tissue engineering, Ocular disease, regenerative medicine, retinal disease*

INTRODUCTION

Our eyes, which serve as the openings to the outside world, give us data regarding our surroundings every 20 milliseconds, enabling us to recognize objects, motions, and a wide range of color tones. The retina, a layer of nervous tissue that includes above 100 million rod and 6 million cone photoreceptors in humans, is in charge of perceiving and integrating sensory data (Rehman et al., 2018).

The retina has two extra neuronal layers that are located below the photoreceptor layer. One of these layers contains horizontal cells (HCs), bipolar cells (BCs), and amacrine cells (ACs), and the other contains displaced ACs and retinal ganglion cells (RGCs). The axonal and dendritic events of the neighboring neurons create two plexiform layers in between those layers, creating a special environment for the establishment of horizontal and vertical synaptic networks through the tissue (Mahabadi et al., 2021).

Retinal cytoarchitecture depends on Mueller glial cells due to the lack of an extracellular matrix, which is similar to other areas of the central nervous system (MGs). In addition to providing structural support, 2 MGs are crucial for maintaining a healthy balance of neurotrans-mitters, trophic factors, and compounds because they extend complex cellular pathways from the inner to the outer limiting membrane (ILM/OLM) and across both plexiform layers (Liu et al., 2021).

Considering the enormous structural intricacy, retinal development is highly regulated and evolutionary conserved. The retinal pigment epithelium (RPE) and the neural retina are two distinct regions that form upon the stimulation of the eye field. In the latter, the unique layering of the retina is shaped in an inside-out manner by the growth, differentiation, and interkinetic nuclear migration of retinal progenitor cells (RPCs) (Cheng et al., 2022).

All subgroups of retinal neurons and MGs are created during this process from a single RPC community, but astrocytes and microglia present

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in the mature retina are not created from RPCs. RGCs are created first during neurogenesis, followed by ACs and HCs, and then cone photoreceptors. Along with MG cells, rod photoreceptors, and BCs are produced last and, in some species, only reach full maturity after delivery.

Interestingly, whereas neurogenesis only persists for limited hours in lower animals, it can last for days or even weeks in rodents, pigs, primates, and humans (Amrein et al., 2011). In higher animals, the end of retinogenesis occurs simultaneously with the full reduction in RPCs. On the other hand, RPCs are limited to the ciliary in lower vertebrates (Amrein et al., 2011).

From this moment on, only lower vertebrates undergo one of three processes for intrinsic regeneration following the deterioration of retinal neurons, glia, or RPE: Mueller glial cells can either: (1) reenter the cell cycle; (2) reactivate growth within RPC in the CMZ; or (3) dedifferentiate from RPEs into RPCs (Willardsen et al., 2014).

The ability of MGs to regenerate in higher vertebrates appears to be diminished, and despite recent research showing that MG-specific overexpression of ASCL1 and histone deacetylase prohibition can restore this ability in young mice, the retina of higher vertebrates is still inherently prone to disease and damage (Fan et al., 2016).

Neurodegenerative ailments, including glaucoma and age-related macular degeneration (AMD), are caused by extra stress or insult in addition to the continuous, age-associated loss of neurons (Bhattacharyya et al., 2022).

According to the National Eye Institute, by 2050, there will be twice as many people suffering from neurodegenerative diseases, necessitating more suitable care (Meleth et al., 2011). By 2020, 196 million people are expected to be affected by AMD alone, which has an 8.7% worldwide prevalence (45-85 years old) (Wang, 2020). Glaucoma is expected to influence 76 million individuals globally. Both circumstances' symptoms can presently be controlled for long years, but the causative neurodegeneration that causes the progressive loss of vision is not possible to be stopped (Smith, 2017).

Cell/tissue replacement has recently emerged as an apparent method to stop damage progression and restore formerly lost vision, thanks to developments in stem cell biology. The earliest clinical trials in the area of cell-based treatment have been conducted as a result of ongoing partnerships between basic scientists and active ophthalmologists, with further clinical studies in the upcoming years. In the current paper, we will highlight the advancements and successes of regenerative medicine.

Biomaterials for regenerative ophthalmology

Collagen

The most prevalent element of extracellular tissue is collagen (ECM). For the best transparency, refractive, and mechanical properties, corneal collagen is extremely organized, and its fibrils are grouped with regular spacing and alignment. Majumdar et al. (2018) measured the cornea's power, strength, and elastic elasticity (Majumdar et al., 2018). Therefore, cross-linked collagen scaffolds that imitate the natural corneal stroma have been applied a lot in corneal regenerative medicine, along with collagen and other collagen-based strategies (Goodarzi et al., 2019).

Utilizing collagen, common tissue engineering techniques use hydrogels, sponges, films, and enhanced substrates. A conventional method based on solubilized collagen is the use of collagen hydrogels. These platforms are not sufficiently sturdy, though. Some cross-linking substances may break down in living things and cause cytotoxicity (Spoerl et al., 2007). In contrast, the microstructures found in collagen sponges and films are better in the context of physiochemical characteristics.

Gels constructed from fibrillar collagen are known as collagen hydrogels. To create firm, rigid shapes, crosslinking is required for all collagen hydrogels (Liu et al., 2019). DC/N-hydroxysuccinimide (NHS)-cross-linked recombinant human collagen (RHC) type III scaffolds were the first to be implanted in patients by Fagerholm et al. (2014). This led to the regeneration of corneal epithelial with the generation of subepithelial nerves and the proliferation of stromal cells in scaffolds. Additionally, 24-month follow-up tests confirmed that all patients' ocular implants remained stable

and avascular and that their tear film had returned.

A permeable collagen fibril network makes up collagen sponges. Collagen sponge production makes it easier to regulate porosity and strength. As collagen sponges, fibrillar sponges, and type I collagen have both been utilized. The primary benefit of bovine collagen type I is that it is porous, allowing corneal stromal cells to enter corneal scaffolds and enhance scaffold remodeling in animal models. Compared to collagen hydrogels, collagen sponges have a considerably greater light transmission. Additionally, they are preferred for stromal matrix repair over collagen hydrogels.

Gelatin

Gelatin is made of collagen after it is hydrolyzed. It is mainly used in three different areas for the engineering of regenerative eye tissue: bioadhesives, cell-sheet carriers, and structural scaffolds (Rose et al., 2014). Gelatin has recently been used in regenerative eye tissue engineering. Gelatin is primarily used as cell-sheet carriers and structural supports in implantable materials. For the repair of optic tissue, 3D printing technologies in terms of gelatin-based 3D tissue models are advancing quickly.

Animal collagens can be used to make gelatin. Additionally, it can be produced as type A gelatin using alkaline pre-treatment and type B gelatin by acidic pre-treatment (Chancharern et al., 2016).

The ocular and limbal epithelium uses gelatin. In a rabbit model, the use of a membrane made of gelatin, HA, and carboxymethyl chitosan (CMCTS) as an epithelial transplantation scaffold led to successful ocular wound healing. Research might provide a novel outlook in light of the pressing need for the creation of an ideal scaffold for corneal regeneration.

The use of gelatin in the ocular stroma. The primary difficulty in producing a fibrous matrix from a single, robust, and entirely transparent structure is sparsely populating it with the proper nerve fibers and dormant keratocytes. Glutaraldehyde cross-linked gelatin can promote fibroblast adhesion and ECM deposition in vivo. It is also being implanted into the corneal stromal pocket of rabbits (Angunawela et al., 2012). Gelatin/ascorbic acid cryogels as keratocyte carriers were found to be biocompatible, stable, and cytoprotective constructs (He, Wang et al., 2021).

The ocular endothelium uses gelatin. The possibility of a gelatin carrier for endothelial sheet. In this study, the intraocular pressure (IOP) and corneal thickness of the human corneal endothelial cell-gelatin implantation were found to be comparable to those of the healthy cornea. For the transport of cultured human corneal endothelial cells into the eye's anterior chamber, in another study heparin-modified gelatin scaffolds were developed (Niu et al., 2014). These scaffolds, which have been altered to ingest and then release growth factors, might work well as cadaveric corneal transplant substitutes.

Chitosan

Chitosan (CS), a naturally occurring, biodegradable linear polymer with a variety of biological activities, plentiful sources, and generally stable physicochemical characteristics, is frequently used in biomedical applications. CS-based delivery materials provide significant benefits over traditional drug delivery systems in combating ocular problems (Mahmoud et al., 2011) (both local and systemic) because of their unique physiological barriers.

Glucosamine and N-acetylglucosamine molecules make up the CS family of linear polysaccharides, which are connected by (1-4) glycosidic links. Chitin which is typically used in its partial deacetylation form is a natural polysaccharide (Heustis et al., 2012). The cell walls of fungi and the carapace of crustaceans like prawns and crabs are both rich in chitin. Chitin from natural sources must first be freed from proteins and minerals. The key elements influencing the characteristics of CS are its average molecular weight and degree of deacetylation, which typically ranges from 66% to 95%. (3.8–20 kD).

Although CS has low alkalinity, it has high hydrophilicity, is water-insoluble, and is stable in both neutral and alkaline conditions. The amino groups of CS are protonated in diluted aqueous acidic solutions, which aids in the substance's breakdown. As a solvent, an acetic acid buffer between 1% and 3% is typically used. It has been possible to alter CS chemically through a number of processes, including carboxymethylation,

reductive amination with phosphorylcholine glyceraldehyde, carboxyethylation, sulfation, N- or O-acylation, and quaternization.

Strong plasticity in CS allows it to be transformed into a variety of shapes, including filaments, gels, microspheres/microcapsules, and micro/nanoparticles. Additionally, it has a lot of functional groups, like free hydroxyl or amino groups, in its construction as well as surface charges that allow it to variably absorb or encapsulate medications with various properties. Additionally, the addition of CS has no impact on the physicochemical characteristics of medicines. CS has an outstanding biological adhesion, coagulation capability, and immune-inducing function in ocular mucosa due to its powerful biological adhesion and instantaneous intercellular permeability (Sun et al., 2022).

Controlled drug release is made possible by CS nanoparticles, which enhance drug durability, solubility, and effectiveness while lowering toxicity. The drug release from CS nanoparticles is controlled by several processes, including drug diffusion, polymer swelling, drug diffusion through the polymeric matrix, and polymer erosion or degradation. Drug diffusion from the polymer surface and polymer swelling, which forms pores, are thought to be responsible for the early liberation of drugs from CS nanoparticles. Additionally, due to their stability, CS nanoparticles display pH-dependent drug release.

CS nanoparticle-related ocular drug delivery can substantially enhance the bioavailability of drugs in the eye when compared to conventional delivery methods (Janagam et al., 2017). Additionally, pH-responsive, thermosensitive, and ion-sensitive CS-based hydrogels are possible. One instance is the management of ocular hypertension, a major glaucoma risk factor (for additional instances, see the section on smart biomaterials). The drawbacks of traditional ocular therapies include their quick clearance and low ocular bioavailability. Antiglaucoma medications must therefore be used frequently and over an extended period, which leads to the formation of local side effects and non-adherence - one of the main reasons why treatments fail.

Hyaluronan (HA)

HA as an unbranched polysaccharide macromolecule, contains repeats of N-acetyl glucosamine and glucuronic acid. HA is the most abundant component of the ECM weighing in the range of 0.1 to >2 million Da. HA is the key element of diverse cellular processes such as wound repair, regeneration, matrix organization, and signaling cascades.

Furthermore, it has exceptional physicochemical features, such as high biocompatibility, biodegradability, mucoadhesive, and viscoelasticity.

This has led to the development of exogenous HA as an excellent drug delivery system.

Chen et al. developed a HA hydrogel scaffold-based xeno-free culture method for the ex vivo cultivation of human cornea epithelial stem cells (Chen et al., 2017) in which there is no need for allogenic or heterogenic biological products, such as transmissible diseases, tumorigenesis, the acceleration of immunologic rejection, or biological diversity (e.g., fetal bovine serum, human amniotic membrane, and murine feeder cells). Using this innovative culture method, a native-like corneal comparable construct with proliferative potential is available. In another study gelatin, carboxymethyl CS, and HA were used to create the best scaffold for growing main rabbit CEpCs.

In corneal alkali-burned rabbits, the biodegradable, and transparent, composite membrane for CEpC binding and growth was successfully implanted. In place of high-quality donor cornea transplantation, HA-based hydrogels crosslinked with hydrazine were used for the therapeutic delivery of adipose stem cells to regenerate injured corneal stromal tissues (Koivusalo et al., 2018).

Despite HA's benefits as a substance for scaffolds, using HA scaffolds has led to some unfavorable effects. The exterior of HA scaffolds might take up different body proteins and trigger inflammatory reactions, which in turn cause denaturation. Furthermore, due to HA's big molecular size, inflammation brought on by HA scaffolds cannot be eliminated by macrophage phagocytosis. As a result, HA scaffolds are rarely used in regions with increased blood flow (e.g., retina and choroid). It is necessary to conduct additional research to expand their utility.

The anti-inflammatory properties of HA, along with its favorable biocompatibility and biodegradability, make it a popular choice for slow-release liquid chemical delivery and nanotherapy. In order to stop excessive fibroblast proliferation and scarring after glaucoma filtration surgery, Shao et al. (2011) suggested a HA film as a vehicle for the slow release of LDL-MMC-CS nanoparticles at the subconjunctival filtering site (Shao et al., 2011). Similarly to this, Huang et al. (2018) showed how to successfully treat DED in rabbits by reducing inflammation using gelatin-epigallocatechin gallate nanoparticles and HA eye drops (Huang et al., 2018).

Products of platelets

Platelet procoagulants contain significant amounts of cytokines and growth factors that are necessary for tissue regeneration and can stop blood loss at the location of a vessel injury. Platelet derivatives are described as preparations produced from autologous or allogeneic platelets that have a greater platelet concentration than was seen at baseline. Platelet gel, platelet-rich plasma, platelet-rich fibrin, and platelet eye drops, are the made products. To encourage and hasten tissue repair, RM practitioners frequently use these preparations. The structure, composition, growth factors, and cytokine concentrations of these compounds vary.

The implementation of blood and its derivatives in ophthalmology is not novel (Giannaccare et al., 2020). In the past, using blood was items on the surface of the eye were mentioned in the Ebers Papyrus, which dates back 3,000 years. Initially, autologous serum eye drops (SEDs) were used to treat patients with DED, and a mobile ocular perfusion pump was applied to administer autologous serum or plasma to the ocular surface of the eyes injured with chemical burns (Giannaccare et al., 2020).

The concept of concentrating and using platelets as a treatment opportunity has steadily gained ground as the research in platelet physiology and pathology has advanced. In reality, a fibrin gel with and without platelets was first presented as a biomaterial with hemostatic and adhesive possessions in the early 1990s (Peng et al., 2021). Platelet-rich preparations were intended to take the place of blood clots as the original justification for platelet goods. Large quantities of proteins and growth factors are secreted by activated platelets. This local environment promotes tissue regeneration mechanisms.

The typical method for making platelet variants involves drawing blood and centrifuging it. Although there are numerous preparations available, none have yet received widespread acceptance. The release and effectiveness of PDGF may undoubtedly be impacted by variations in platelet preparation techniques (Reigstad et al., 2005).

The conditions for centrifugation, the quantity and quality of platelets, exogenous platelet preactivation, the break between injections and the quantity of treatments required are some of their manufacturing factors. Centrifugation is a crucial factor that significantly affects quality and differs greatly in terms of duration and speed. High centrifugal forces during preparation are able to stimulate platelets, reducing platelet activity and function. Additionally, there is debate over the ideal platelet percentage.

The present method for making platelet-rich plasma entails collecting blood in an acid, citrate, and glucose solution and centrifuging it. To produce platelet pellets and platelet-poor plasma, a second, quicker centrifugation is performed on platelet-rich plasma (PRP) (PPP). Thrombin, the most effective platelet activator, causes PRP to produce growth factors. There is a significant risk of coagulopathy when bovine thrombin is administered in clinical settings because it can rarely cause advances in the production of antibodies to coagulation factor V, factor XI, and human thrombin.

The decision between autologous and allogeneic platelet derivatives is crucial in therapeutic practice. The use of autologous platelet derivatives eludes the ethical consequences related to the risk of exposing patients to allogeneic blood constituents in the absence of a pathogen inactivation process, especially in nations with high infection rates and restricted donor testing. Contamination during gathering and processing poses the lone infection risk connected to autologous products (De Pascale et al., 2015). Additionally, patients might find

autologous goods more agreeable. Individual biologic variations are another drawback of allogeneic platelet derivatives made from healthy donor blood via standardized methods used at blood transfusion services.

Stem cells

Stem cells can self-renew and can differentiate into different kinds of cells. These cells can experience limitless self-renewal, exist in an unspecialized state, and are able to differentiate into various cell types, which are their three defining characteristics. Stem cells can be categorized into embryonic stem cells (ESCs), neonatal stem cells, and adult stem cells depending on the source (ASCs). The embryo-derived stem cells, including ESCs, amniotic stem cells, and umbilical tissue-derived stem cells, are the subject of the following part. These pluripotent cells are a very hopeful source for future treatment options for various eye diseases.

Gene thetrapy

Voretigene Neparvovec, which contains the RPE65 photoisomerase gene delivered to the retina through an adeno-associated virus (AAV)55, was the first viral gene therapy authorized for any neurologic condition. The US FDA authorized this biopharmaceutical in 2017. The congenital blinding illness Leber congenital amaurosis' RPE65-deficient variant is treated with subretinally administered virus injections (LCA). In controlled clinical trials, the treatment restored functional vision in young patients with this condition, demonstrating the viability of ocular gene therapy. Nevertheless, this particular form of gene therapy is focused on a single gene.

Replacement treatments are difficult because retinitis pigmentosa has been linked to more than 60 genes. Intraocular gene therapy may have extra drawbacks, such as persistent degeneration in the face of the treatment. However, this strategy is still hopeful for some inherited retinal illnesses, whether it be through replacement or immune system activation in reaction to the viral vector 58. Utilizing viral-based gene therapy is an alternative method for expressing trophic factors that indicate proliferation and survival and whose expression might leisurely the degenerative procedure.

Such a strategy has been shown to be successful in animal models for some trophic factors, including ciliary neurotrophic factor (CNTF), pigment epithelial-derived factor, brain-derived neurotrophic factor, and rod-derived cone viability factor, though anatomy preservation is typically more important than visual function preservation (Hojo et al., 2004).

In a different method of gene therapy for vision restoration known as optogenetics, phototransducing opsins, which turn light into electrical impulses, are inserted into the bipolar or retinal ganglion cells that are still present in outer retinal degeneration using viral vectors. Seven transmembrane proteins that gate cation or anion channels in response to light exposure, derived from microbes, are packaged in AAV under either a general promoter or a promoter unique to retinal ganglion cells.

There are currently at minimum 3 clinical studies that use channelopsins delivery through gene therapy. Since channelopsins are less light-sensitive than natural human opsins, they must be expressed widely using the best gene therapy vectors. This approach holds great potential for vision restoration, but it also carries the theoretical danger of immune reactions to foreign proteins.

It has been demonstrated that a comparable strategy utilizing the human G-protein-coupled receptors rhodopsin or cone opsin can restore visual function in animals suffering from outer retinal degeneration. Due to G-protein amplification, mammalian opsins are more sensitive than channelopsins and, as natural proteins, do not trigger immune reactions. Clinical studies involving humans are being developed for this strategy.

Animal models of outer retinal degeneration have also demonstrated the effectiveness of eyesight restoration using azobenzene-based photoswitches. Through photoisomerization of an azobenzene moiety that is covalently linked, voltage-gated potassium channel-blocking drugs are made active in light using this method (Bregestovski et al., 2019). These substances make retinal ganglion cells immediately photosensitive after intravitreal injection (Bregestovski et al., 2019). This strategy prevents the irreversibility of gene therapy but calls for multiple sessions.

In recent years, numerous basic challenges in

cell production and retinal disease modeling that stood in the way of the clinic have been overcome. The present push in the arena is towards clinical translation, critical assessment of functional outcome measures, and the integration of combinational treatments. The most challenging fundamental problems, such as synaptogenesis and retinal rewiring, may be approached by considering developmental theories.

While the experience garnered from RPE is presently influencing the clinical translation of retinal cell replacement, overall critical advancements that would transform the replacement of retinal neurons from a laboratory model to a clinically relevant treatment are still missing. The results of cell transplantation into animal models of retinal disease have generated a lot of excitement, but the next stages towards human translation must be taken carefully. Planning and carrying out clinical trials must be based on the all-out possible inclusion of objective metrics for safety, efficacy, and mechanism of action in light of the identification of artifacts like cytoplasmic transfer and the ongoing quest to separate neuroprotective effects from functional improvements attributed to real cell replacement.

Declaration of competing interest

The authors declare no financial interests or personal relationships.

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