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The Role of Retinal Pigment Epithelium in the Pathogenesis and Treatment of Age Related Macular Degeneration

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Abstract

Retinal pigment epithelium (RPE) has a fundamental role in preserving retinal health via supporting and protection of photoreceptors, establishment of the outer blood-retinal barrier, and engaging in many biochemical reactions. Therefore, RPE malfunction and destruction in disorders such as age-related macular degeneration can eventually result in outer retinal degeneration and permanent loss of vision. Cell-based and gene-based therapies to rectify RPE function are novel approaches to treat disorders, which otherwise considered untreatable. These strategies are particularly effective in patients who still have an acceptable retinal function, and thus should be applied in the early stages of the disease. There are a variety of approaches for RPE replacement therapy and many promising target gene therapy. There is still a long way to establish the best method in this regard. This review focused on the role of RPE in the pathogenesis of retinal disorders and also the role of cell or gene therapy in the management of retinal disorders.

Keywords: ARMD, Retinal degeneration, RPE, Cell therapy, Gene therapy

Introduction

There is a broad range of ocular disorders that are hard to cure and might end in blindness. Age-related macular degeneration (ARMD) is one of the fairly common ophthalmic diseases, which affects central retina in people over 65 years and is more prevalent in industrial societies (1). It is estimated that about 8.7% of all blindness all over the world is caused by ARMD (2). Besides, ARMD has a huge impact on a patient's life. Moderate ARMD could lead to a 40% decline in quality of life, very much like an advanced cardiac or renal disease (3). The main cellular feature of ARMD is RPE degeneration (4). That's why RPE cells have drawn significant attention in recent years. RPE cells are essential for the optimal activity of photoreceptors and phagocytosis of their outer segments (5). They are constantly exposed to a high level of oxidative stress from light energy and high oxygen pressure. There are specialized mechanisms in RPE cells to reduce damages occurred to cell macromolecules. These include enzymatic and non-enzymatic antioxidants, and identification of damaged lipids, proteins, and nucleic acids, and their repair and replacement (5). However, aging can lead to cumulative irreversible changes in RPEs over the years, which may cause RPEs dysfunction. In the elderly, about 3% of RPE cells are destroyed each year, which leads to increased metabolic load on adjacent RPE cells (6). The appearance of polymorphic and non-cellular deposits between RPE cell layer and Bruch's membrane is one of the clinical signs that occur in the early stages of ARMD (7). Drusens commonly appear bilaterally, but sometimes maybe initially found in only one eye. Drusens alone does not affect the vision; however, they induce a chronic inflammatory response and eventually lead to damaged RPE, geographic atrophy, and expression of VEGF cytokines. Abnormal choroidal angiogenesis might ensue in some cases and is often associated with increased permeability and choroidal vascular fragility. Subsequently, significant visual impairment may result from subretinal hemorrhage, extracellular fluid accumulation, and fibrotic scars (7, 8).

RPE cells

Rod and cone photoreceptors are supported by RPE, which is intimately attached to the outer retina, and protects and feeds retinal photoreceptors. RPEs are composed of compact hexagonal cells, appeared as a columnar cubic monolayer, and the cells are full of pigmented granules. Just like other epithelial cells, the RPE cells are polar, and their organelles are placed across a basolateral axis along the cells (9). Tight junctions, which are the fundamental part of the outer blood-retina barrier, guarantee polar distribution of ionic channels and membrane receptors on the basolateral and apical surfaces of the RPE (10).

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The apical membrane of RPE cells is toward the outer part of photoreceptor cells and their basolateral membrane faces Bruch's membrane. Bruch's membrane is a pentalaminar layer with 1-4 µm of thickness (11). The extracellular media of RPE cells is called subretinal space and is filled with an inter-photoreceptor matrix (IPM) (12). Specialized microvilli of RPE cells extrude into subretinal space and thus interact with cone and rod photoreceptors through IPM, providing for retinal consistency and durability. Macular RPEs are slimmer and taller than those located in the surrounding area (10-14 µm width compared with 60 µm). This indicates an increase in RPE cell density in this area (from 1500 in the periphery to 4500 cells per mm2 in the macula). The number of photoreceptors surrounded by each RPE varies depending on their position in the retina and age of the patient. It has been estimated that a single RPE cell could interact with 20-55 photoreceptors (6). One of the main features of RPEs is their pigmentation due to the presence of melanin granules, called melanosomes, in the apical zone. It seems that deficiency in melanin pigment is one of the features of ARMD (13). Lipofuscin accumulation, an excretory metabolic of rod outer segment, is another important RPE change related to aging (14). Many stages of melanin synthesis and maturation are claimed to be completed by the age of 2, yet continuous melanogenesis throughout life is a controversial issue (15). It has been demonstrated that degeneration of melanin in RPE cells decreases with age, and this could be due to oxidation-induced degeneration. Besides, several aging changes occur in melanin, which results in decreased activity (6). Melanogenesis has a key role in the development and evolution of neural retina. Melanin inhibits opposing light scattering, absorbs different wavelengths of light, traps free radicals, and has antioxidant activity and interaction with many chemicals and drugs. Besides, the melanin content of RPE substrates for transplantation is considered to be of great importance for the long-lasting efficiency of cell therapy (6, 16). RPE cells absorb nutrients such as glucose, retinol, and fatty acids from the blood and pass it to retinal cells. Retinol is one of the most important substrates in the visual cycle, which frequently exchanges between RPE and photoreceptors (17). RPE secretes a broad spectrum of growth factors such as FGF1, 2, 5, TGF-β, IGF-1, CNTF, PDGF, VEGF, LEDGF, interleukins, PEDF, and TIMP 1, 2, and 3 (18). Previous reports showed that RPE has immunosuppressive activity and can suppress CD4+ and CD8+ T-cells (19). RPE cells can also induce apoptosis in Jurkat T-cells (19). Since RPE cells are physically separated from the blood via Bruch's membrane, the mentioned inhibitory effect is probably due to the secretion of soluble factors rather than direct interaction of RPE with blood cells (18, 19).

RPE as a neural progenitor cell source

RPE cells are among the best-known cell sources which can act as neural progenitor cells in vitro (20). Accordingly, there is evidence that shows RPE cells express neural progenitor markers. RPE cells have the potential of proliferation and regeneration in vitro and in response to different substrates (including serum and amniotic fluid) (20, 21). In addition, the ability of RPE cells to differentiate into retinal neural cells and photoreceptors has been reported previously (20-23). It seems that RPE cells are a promising candidate for retinal cell replacement therapy in degenerative retinal diseases such as ARMD (24). *Pax6* and *CHX10* are of the most important genes involved in controlling the retinal neural-progenitor character in RPE cells (25).

PAX6

PAX6 transcription factor is a member of *the PAX* multigene family. *PAX* (paired box) genes are a family of tissue-specific transcription factors having a paired box and a complete or partial homeodomain. PAX proteins are vital for embryonic development of specific tissues. PAX6 protein is one of the transcription factors that is expressed in the cell nucleus. Gene expression depends on different concentrations of PAX proteins (26-28). There are 4 well defined groups of *PAX* genes: *PAX* group 1 (*PAX* 1 and 9), *PAX* group 2 (*PAX* 2, 5 and 8), *PAX* group 3 (*PAX* 3 and 7) and *PAX* group 4 (*PAX* 4 and 6). Among all, *PAX6* gene has been studied more deeply and considered as the master control gene for the development of the eye, sensory organs, and epidermal and neural tissues originated from ectoderm (26-29). This transcription factor is well known because of its overexpression in the ectopic eye and its medical importance in heterozygous mutated *PAX6* which underlies a wide range of eye defects and abnormalities such as aniridia (30, 31). PAX6 protein activity is conserved among bilaterian species. However, the genomic organization of *PAX6* loci, such as the number and distribution of exons, cis-regulatory elements, and sites for initiation of transcription, are significantly different between various species. In humans, *PAX6* gene is located on the short arm of chromosome 11 (11p13) within the AN2 region. *PAX6* locus produces 2 different protein isoforms (*PAX6* and *PAX6* $^{(+5a)}$). *PAX6* is transcribed to a 2.7 kb mRNA and then results in a 422 amino acid protein including a paired box, homeobox, and a C-terminal proline-serine-threonine (PST) domain (32). Recent studies have shown that the *PAX6* gene is medically important and can be applied as a tool for regeneration of eye tissues. Evidence is implying that artificial induction of *PAX6* expression in damaged eye tissue can trigger cell regeneration and tissue repair (33). *Pax6* expression plays a pivotal role in guiding retinal cells toward progenitor fate.

CHX10

CHX10 which is also named *VSX-2* encodes for visual system homeobox 2 protein (34). It is consisted of 361 amino acids and has a molecular weight of 39 kDa in humans. *CHX10* is homologous to *Ceh-10* (C. Elegans neuronal expressed homeobox gene) in vertebrates. There are 4 regions in *CHX10* gene, which are found in humans, mouse, fish, drosophila, and nematode: octapeptide motif including 8 aminoacids FGIQEILG, homeodomain region including 60 amino acids, a helix-turn-helix motif for DNA binding (QAR domain), and CVC domain (35). In humans, *CHX10* is located on the long arm of chromosome 14 (14q243) (36). *CHX10* is expressed in retinal progenitor cells from the early stages of optic disk formation. In adults the expression of this gene is limited to bipolar and some Muller cells (34, 37). CHX10 protein is a retinal specific transcription factor expressed in the nucleus. *CHX10* mutation causes cataract, microphthalmia, and lens abnormality (36, 38). This protein has a key role in the morphogenesis and specificity of the sensory retina. Pieces of evidence are showing that *CHX10* also has a role in the development of retinal inner layer cells and particularly bipolar cells. *CHX10* seems to act as a

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gatekeeper to run retinal progenitor program (39). *CHX10* is suggested to bind to MITF transcription factor and prevent it from regulation the genes involved in pigmentation and differentiation (39).

Table 1. A summary of reports on RPE replacement clinical trials for the treatment of ARMD

Cell type transplanted	Animal model/ clinical study	Disease for treatment	Result/outcome	Cell delivery method	Reference
hESC derived RPE	Clinical trials on 2 patients Clinicaltrials.gov: NCT01345006 and NCT01344993	Stargardt's disease, dry ARMD	Slight improvements in visual acuity in both patients, no tumorigenicity or apparent rejection after 4 months	Cell solution transplantation	45
hESC derived RPE	18 patients (phase 1 and 2 clinical trial) Clinicaltrials.gov: NCT01345006 and NCT01344993	ARMD and Stargardt's disease	Safety concerns were met in a 22 months follow up (no major adverse events or immune-reactions was noted)	Cell suspension transplantation	46
hESC derived RPE monolayer on a coated, synthetic basement membrane	10 patients (phase 1 clinical trial) Clinicaltrials.gov: NCT01691261	Severe exudative ARMD	Visual acuity was improved, no tumorigenicity was observed, cell safety was approved	Patch transplantation into the subretinal space	47
composite, termed the (CPCB-RPE1 implant), consisting of a polarized monolayer of hESC-RPE on an ultrathin, synthetic parylene substrate	5 patients (phase 1 clinical trial) Clinicaltrials.gov: NCT02590692	non-neovascular ARMD	Visual acuity was improved and hESC-RPE and host photoreceptor integration occurred. No severe adverse effect was observed.	Subretinal implantation	48
Autologous hiPS derived RPE	1 patients Clinical Trials Registry [UMIN-CTR] number, UMIN000011929	neovascular ARMD	The transplanted sheet remained intact after 1 year post transplantation, while visual acuity was not changed, and cystoid macular edema was present	Subretinal transplantation	49
hESC derived RPE	4 patients Clinicaltrials.gov: NCT01625559 and NCT01674829	two with dry age-related macular degeneration and two with Stargardt macular dystrophy	Visual acuity was improved, no tumorigenicity was observed, cell safety was approved	Subretinal transplantation	50
autologous RPE-choroid sheet and RPE cell suspension	24 patients clinicaltrials.gov: NCT00401713	exsudative AMD	both RPE transplantation techniques led to comparable anatomical and functional outcome	sheet transplantation or cell suspension transplantation	51

ARMD: age related macular degeneration, **CPCB-RPE1**: California Project to Cure Blindness–Retinal Pigment Epithelium 1, **hESC**: human embryonic stem cell, **hiPS**: human induced pluripotent stem cell, **RPE**: retinal pigmented epithelium, **RCS rat**: Royal College of Surgeons rat,

New strategies for ARMD treatment

Different methods for the treatment of ARMD have been introduced in recent years. The efficacy and safety of laser photocoagulation, photodynamic therapy, and anti-angiogenic drugs have been verified for wet type ARMD (40). On the other hand, there is no effective treatment for advanced stages of dry ARMD and also for destructive sequels of wet ARMD, despite successful management of choroidal neovascularization. Therefore, there is a great demand for developing novel treatments to be applied as an accomplishment to other strategies. Cell-based therapy in ophthalmology is an optimistic and fast-growing field. Newly emerged techniques for imaging and surgical technologies have provided the basis for further advance cell-based therapies for ocular disorders (41). It has been shown that replacing dysfunctional or dead RPEs with healthy RPEs can preserve vision via the rescuing of dying photoreceptors in ARMD patients (42). Transplanting of autologous healthy RPE from the peripheral retina into the submacular area in patients with macular degeneration showed some degrees of visual recovery (43). However, there are some limitations associated with cell replacement strategies such as very restricted sources of cells and the possibility to contain predisposing genetic defects which can result in continued retinal damage. Stem cell-derived RPE is a well-controlled and a suitable source of RPE to be considered for replacement therapy (44). Differentiation of RPE from induced pluripotent stem cells (iPSC-RPE) and human embryonic stem cells (hESC-RPE) has also made a potentially unlimited source for replacement of dysfunctional RPE. It has

been shown that such cells can accommodate the degenerating retina and lead to functional and anatomic improvements (42). Table 1 shows a summary of references number (45-51) which have reported the result of completed clinical trials of cell-based RPE replacement for the treatment of ARMD. However, we still face several challenges in stem cell-based therapies such as hESC related ethical issues, clinical grade manufacturing, and batch to batch variation of cell substrates which should be overcome in future investigations.

Conclusion

Recent investigations in cellular and molecular aspects of RPE cells have made RPEs as an optimistic source for cell-based and gene-based therapy of ARMD. The great potential of hESC and hiPS derived RPEs in the regeneration of damaged retina has been approved in animal models and clinical examinations. Besides RPEs are promising targets for gene transfer and treatment of ocular gene deficiencies. Although many concerns have remained to be approved considering the safety and efficacy of the newly introduced strategies in cell replacement and gene therapy of retinal diseases.

Ethics approval and consent to participate

Not applicable.

Conflict of interest

The authors declare that there is no conflict of interest.

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