Review Article

Amniotic membrane as a novel treatment in age-related macular degeneration: a narrative review

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Abstract: Age-related macular degeneration (ARMD), one of the most common causes of blindness, should be considered more due to its exponential increase in the coming 20 years as a result of increasing the age of the population. Whereas more recent studies offered newer scaling systems for ARMD, traditionally it is classified as the early and late stages. The main injury in this disease occurred in retinal pigment epithelium (RPE) and the retina. RPE cells have a crucial role in hemostasis and supporting photoreceptors. In the early stages, damages to RPE are minimal and mainly no treatment is needed because most patients are asymptomatic. However, in the late stages, RPE impairment may lead to the invasion of choroidal vessels into the retina. Although anti-angiogenic agents can inhibit this abnormal growth of blood vessels, they cannot stop it completely, and finally, total loss of retinal cells may occur (geographical atrophy). Since this prevalent disease has not had any cure yet, the concept of substituting the RPE cells should be considered. Repairing the injury to central nervous system cells is almost impossible because the regenerative capacity of these cells is limited. Recently, the use of regenerative substitutes has been suggested to replace damaged tissues. Amniotic membrane (AM) has been raised as a suitable substitute for damaged RPE cells due to all of its unique properties: pluripotency, anti-angiogenic effect, and anti-inflammatory effect. Based on the few studies that have been published so far, it seems that the use of this membrane in the treatment of ARMD can be helpful, but more studies are needed.

Keywords: Age-related macular degeneration (ARMD); amniotic membrane transplant; retinal pigment epithelium (RPE)

Received: 05 March 2021; Accepted: 12 November 2021; Published: 30 December 2021.
doi: 10.21037/aes-21-17
View this article at: https://dx.doi.org/10.21037/aes-21-17

Background

Age-related macular degeneration (ARMD) is a progressive neurodegenerative disease affecting the retina and retinal pigment epitheliums (RPEs) as well as the function and structure of the macula (1-3).

The disease is diagnosed by clinical examination. Early in the disease, when it is usually asymptomatic, the presence of drusens of varying sizes (hard (or small), medium (>63 mm), and large (>125 mm) and changes to the retinal pigmentary epithelium is diagnostic. As the disease progresses, it may result in decreased vision due to choroidal neovascularization (CNV) or geographic atrophy (GA) (4).

In advanced societies, ARMD ranks among the top three causes of blindness worldwide (5).

According to estimates, there will be 196 million in the year 2020 and 288 million in the year 2040 suffering from all stages of ARMD. The increase in world population and the aging of the population contributes to the exponential increase in the prevalence of this disease (6,7).

Though only 10–15% of people with ARMD develop

CNV, it causes 90% of severe vision loss (8).

The pathophysiology of this multifactorial complex disease is still not well understood. Interaction between genetic and environmental factors are playing a major role in the pathogenesis of this disease (9,10).

In the early stages of ARMD, vision usually is not affected. There is no effective treatment for this stage, but taking a daily AREDS-2 formulation based on two AREDS studies is the standard approach for reducing the risk of progression from this stage to late-stage by 25% relative to placebo at 5 years for patients with a high risk of progression to the advanced stage (11). Since smoking accelerates the progression of the disease, quitting the habit is one of the best ways to prevent it (11).

Although recent advances in CNV treatment and targeting angiogenesis (inhibiting VEGF production induced by hypoxia) by anti-VEGFs agents have indicated a promising future compared to older therapies, new treatments still need to be developed (12).

Repetitive injections of anti-VEGFs substances may be economically burdensome and be associated with ocular complications (endophthalmitis, retinal detachment, retinal plate tear, intraocular inflammation, etc.). In addition, these drugs do not cure the disease, only delaying the loss of vision. Studies have shown that after beginning injections, vision improves in the first 5–8 years, but vision begins to decline after this improvement during long-term follow-up (12-16). For delayed diseases, such as geographical atrophy, which results in 37% of vision loss, there is no treatment (16). We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/aes-21-17).

Methods

We searched the electronic database of PubMed for studies on AMD published up to September 2020, with the following search terms: ("amniotic membrane" or "human amniotic membrane" or "metabolome" or "amnion") AND ("age-related maculopathy" or "age-related macular degeneration"). Additional articles were selected from searching the reference lists of included studies. We included all designs of studies in English-language.

RPE

The RPE is a single layer of hexagonal pigment cells located just outside the retina. Their basolateral surfaces lie on the Bruch membrane, while their apical surfaces face the outer segments of retinal photoreceptors (17).

These cells play a crucial role in maintaining the health and function of the retina.

(I) The pigment in the RPE cells absorbs excessive light that reaches the retina, protecting it from oxidative damage and preventing photooxidation. These cells prevent oxidative damage via enzymatic antioxidants (superoxide dismutase and catalase), non-enzymatic antioxidants (carotenoids, such as lutein and zeaxanthin), and glutathione and melanin (18).

(II) The proper function and structure of photoreceptors are one of the essential elements in light transduction and normal vision. The retinal proteins and lipids involved in light transduction via the photoreceptor are susceptible to damage by intense light and high oxygen concentrations in the choriocapillaris. The renewal of these substances is accomplished by phagocytosis of the RPE and the redelivery to photoreceptors of important material and exocytosis of other substances to the choriocapillaris (19).

(III) This layer also plays a major role in maintaining the extracellular environment of the outer retina. As well as providing glucose, retinol, ascorbic acid, fatty acids, and other nutrients to the photoreceptors, these cells transport electrolytes, water, and metabolic waste products from the subretinal space to the choroid (18,19).

(IV) Growth factors like fibroblast growth factors (FGF-1, FGF-2, and FGF-5) and transforming growth factor-β (TGF-β), insulin-like growth factor-I (IGF-I) ciliary neurotrophic factor (CNTF), platelet-derived growth factor (PDGF), vascular endothelial growth factors (VEGFs), lens epithelium-derived growth factor (LEDGF), interleukins and pigment epithelium-derived factor (PEDF) are formed and secreted by RPE to keep the choroid and photoreceptors functional and healthy (17).

(V) The RPE plays a significant role in the immune privilege status of the eye by producing and secreting immunosuppressive agents (17,20).

(VI) The RPE also plays a crucial role in the retinoid cycle. After light absorption by rhodopsin, 11-cis-retinal is converted to all-trans-retinal and

phototransduction begins. All-trans-retinal is transformed into all-trans-retinol, then taken up by the RPE, isomerized to 11-cis-retinal, and then transported to the photoreceptors (19).

Bruch membrane

The Bruch membrane is a multi-layered acellular connective tissue located between the RPE and the choriocapillaris. This structure consists of five layers. The RPE basement membrane and the choriocapillaris endothelium basement membrane are the most anterior and posterior layers, respectively. The inner collagenous layer (ICL) and the outer collagenous layer (OCL) are located between these two basement membranes and are separated by the elastic layer (EL) (17).

This membrane facilitates RPE cell migration, adhesion, and differentiation. Furthermore, it regulates molecule and substance diffusion between the RPE and choriocapillaris layer. The Bruch membrane inhibits cellular and vascular migration from the choroid into the subretinal or sub-RPE and vice versa (8,17).

Role of the RPE & Bruch membrane in ARMD

Although the exact mechanism of ARMD is still unknown, multiple lines of evidence point to aging changes of RPE and Bruch membranes as an initiating event.

RPE cells become dysfunctional as they age because of oxidative stress. RPE dysfunction and age-related ultrastructural changes in the Bruch membrane (increase in thickness, fat deposition, collagen crosslinking of collagen layers, drusen formation, basal laminar and linear deposition, calcification, and elastin layer fragmentation) occur years before the clinical signs and the appearance of RPE cell changes on imaging. Age-related RPE and Bruch's membrane changes stimulate chronic low-grade inflammation or parainflammation that causes more damage to RPE cells, thereby creating a vicious cycle. This event amplifies and persists immune system activity against RPE and Bruch's membrane (8,21,22).

RPE cells damage leads to drusenogenesis, a form of extracellular accumulation that lies between RPE and Bruch's membrane. As opposed to the ocular immune privilege, drusen and RPE cells covering drusen are immunoglobulin and complement-reactive. The presence of immune molecules in the drusen and inflammatory cells in Bruch's membrane supports the role of inflammation (23).

The presence of drusens is an early sign of ARMD, a hallmark, as well as a risk factor for its progression (24).

Another evidence for supporting the role of the immune system in ARMD is multiple mutations in the complement cascade, including protective and risk-enhancer genes that play role in ARMD. Mutation in complement component 2 (C2), complement component 3 (C3), complement factor H (CFH), factor B (CFB), and factor I (CFI) are some of these genes (23).

Local inflammation in RPE and Bruch's membrane lead to drusen formation, photoreceptor, and RPE death, and Bruch membrane break and CNV formation (25). In the excised CNV also there are multinucleated giant cells that support the role of inflammation in CNV formation (26). An increasing number of studies have found that inflammation plays an important role in CNV formation. The histopathology of CNV reveals the presence of macrophages, giant cells, and microglia (27-32).

Research has shown that at least one primary event in GA occurs at the RPE cell layer, which causes atrophied and lost photoreceptors, choriocapillaris, and RPE vessels (33).

Researchers have found that the Bruch elastin layer in the macular region differs from that of the retina, making it susceptible to conditions such as CNV, GA, and disciform scars in ARMD patients (8).

Beyond the role of these layers in this disease, if these layers are injured due to CNV formation or during the dry stages of the disease due to the inability of RPE cells to regenerate apoptotic photoreceptor cells, the photoreceptors will not be recovered (34).

Therefore, since there is no treatment to repair photoreceptors or improve the function of RPE cells, and because CNV therapies are ineffective at repairing RPE, and even CNV regression cannot regenerate RPE cells, optimal improvement of vision is not possible (34).

Human amniotic membrane

The human amniotic membrane is a thin semitransparent avascular tissue, envelopes the human fetus and is the innermost layer of fetal membranes. This tissue is composed of three layers: Stromal matrix, basement membrane, and monolayer epithelium (35).

The amniotic membrane has several advantageous properties. These characteristics together make this membrane a promising alternative source for tissue transplantation. The epithelial cells of these membranes originate from epiblast cells, and epiblast cells are

responsible for all three germ layers in the embryo. Therefore, multiple studies have confirmed the pluripotency of these cells (36).

Another amniotic property of membranes is the anti-angiogenic effect. This property can be explained by the physical barrier of this layer, which prevents the growth and migration of endothelial cells. Extracellular proteins such as collagen α2(IV), laminin-1, laminin-5, fibronectin, and collagen type VII also appear to act as angiogenesis inhibitors. Endostatin and thrombospondin-1 are potent anti-angiogenic cytokines secreted by amniotic membrane cells. Some types of matrix metalloproteinase, IL-1 receptor antagonist, collagen XVIII, and IL-10 might also play a role in anti-angiogenesis (37-40).

PEDF is a neurotrophic and anti-angiogenic factor. This molecule is found in high concentrations in ocular tissue like the cornea and vitreous. The molecule was also detected in the amniotic membrane (37,40,41).

Human amniotic membranes on which RPE cell sheets are transplanted may have some advantages over injection of RPE cell suspensions into the vitreous cavity. By secreting more growth factors and cytokines, RPE cells are more resistant to oxidative damage, which can lead to cell death. Human amniotic membranes act similar to the Bruch membrane, which is damaged by some types of ARMD. These factors may explain why this group of eyes has better visual acuity (42).

The amniotic membrane provides the scaffold for the migration of epithelial cells. The scaffold stimulates cell differentiation while inhibiting apoptosis in epithelial cells. The amniotic membrane is more than just a scaffold that accelerates epithelialization during wound healing. The amniotic membrane inhibits the expression of the TGF-β receptor in fibroblasts, resulting in less fibrosis and scarring. It has now been suggested that TGF-β1, -β2, and -β3, TGF-α, epidermal growth factor (EGF), keratocyte growth factor (KGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), and two growth factor receptors (KGFR and HGFR), have found in the amniotic membrane is implicated in wound healing (36).

Secreting substances like IL-10, TGF-β, HGF, prostaglandin E2 (PGE2), human leukocyte antigen (HLA)-G, and indoleamine 2,3-dioxygenase (IDO), as well as interferon (IFN)-γ-activated macrophages apoptosis, induced by down-regulating anti-apoptotic substances (NF-κB and Akt-FKHR) via Amniotic membrane and polymorphonuclear neutrophil apoptosis, are mechanisms involved in the anti-inflammatory effect of the amniotic membrane (43-45).

Amniotic membrane expression of HLAs (HLA-A, HLA-B, HLA-C, and HLA-DR) that cause rejection is minimal, although HLA-G with tolerogenic properties is expressed and reduces the risk of rejection. The low immunogenicity of the amniotic membrane makes it a good candidate for a low-risk graft (34).

Regenerative medicine

The damage to the retina and RPE is irreversible because these cells do not have a good capacity for regeneration (46). The properties of these cells make them difficult to repair or regenerate, and damaged cells are found in many ocular diseases, including ARMD. Because of their properties, there has never been a solution to repair or regenerate these types of cells (46,47). Regenerative medicine is an interdisciplinary field that seeks to find substitutes for damaged tissues to restore function and structure (48). The amniotic membrane is one of these substitutions.

This review article aims to discuss the structure and function of the amniotic membrane, and its role in treating late ARMD.

In vitro studies

A study of RPE cells cultured on an amniotic membrane without epithelium and plastic surface showed that RPE monolayer cells grown on amniotic membrane integrate with the substrate and form intercellular junctions. As with RPE cells, these cells show ultrastructural characteristics such as microvilli on the apical surface and intercellular junctions. Expression of RPE65, CRALBP, bestrophin, and tyrosinase-related genes protein (TRP)-2 and the production of proteins such as VEGF, thrombospondin-1, and pigment epithelium-derived growth factor (PEDGF) was higher in cells cultured on amniotic membrane than in cells cultured on plastic. It was shown that the amniotic membrane is capable of facilitating the proliferation of RPE cells and the expression of genes that are required for retinal homeostasis, and it serves as a suitable surface for transplantation into the subretinal space (49-51). Some researchers reported a marked increase in RPE65, CD68, and VEGF and no change in CRALBP and tyrosinase levels in RPE cells cultured on amniotic membrane compare to the naive RPE cells (52).

In vivo studies

Animal

Since CNV is a non-specific response to Bruch's injury and there is no histological difference between CNV caused by ARMD and other underlying diseases, CNV can be induced with a lesion such as Bruch's perforation.

A study at the University of Copenhagen was conducted by Kiilgaard and colleagues to determine the effect of amniotic membrane subretinal transplantation on RPE cell regrowth and CNV formation. The injection of isotonic NaCl solution into the subretinal space through retinotomy caused retinal detachment and then RPE layer cells were removed from the subretinal spaces causing a rupture in the Bruch layer. In one group consisting of 15 pigs, in addition to the CNV induction technique, the AM without epithelium was transferred to the subretinal space and exposed, whereas, in the other group, only CNV induction was performed.

The microscopic examination of all enucleated eyes revealed evidence of CNV formation and Bruch layer damage. In all of the cases, the vessels remained underneath the membrane, never penetrating it. A successfully placed amniotic membrane that entirely covers the rupture on the Bruch membrane produced lower CNV height than control or a misplaced amniotic membrane.

RPE cells maintain the level of pigmentation of RPE surrounding AMT.

Induction of CNV causes severe inflammation in the retinal layers, especially in the choroid. In this study, inflammation of the retina after CNV induction did not differ significantly between the two groups, but inflammatory cells were less prevalent near AMT, and in cases in which AMT was successfully located and CNV was minimal, inflammatory cells did not increase in number.

In the case of incorrect placement of AMT, which is one of the potential complications of this surgery, the height of CNV did not differ significantly from that of the control group (53).

The injection of AM intravitreally after laser-induced CNV in a rat model showed an increase in CNV thickness compared to the control group. The authors speculated that this effect is related to the pro-angiogenic property of AM (54).

Human

Prof. Rizzo's team hypothesized that human amniotic membrane can regenerate photoreceptors; therefore, they carried out a subretinal human amniotic membrane transplant for 11 patients with low vision secondary to GA or fibro-hemorrhagic subretinal membrane ARMD with a history of multiple anti-VEGF injections.

Their technique involved placing the human amniotic membrane chorion layer toward the RPE after 3-port, 23-gauge transconjunctival pars plana vitrectomy (PPV), retinectomy, and retinal detachment induction. In cases of hemorrhagic ARMD neovascularization was removed after retinal detachment induction. The retinal reattachment was achieved via injection of perfluorocarbon and a retinopexy laser at the borders of the retinectomy.

Patients' follow-up over twelve months demonstrated significant visual acuity improvement. Best-corrected visual acuity (BCVA) improved from 20/2,000 to 20/320 in the GA group, and from 20/2,000 to 20/250 in the hemorrhagic group.

In terms of complications, one patient did not improve his BCVA. This patient suffered choroidal hemorrhage during detachment induction, and human amniotic membrane was positioned extrafoveally. Another complication was cystoid macular edema after successful surgery. Ozurdex® (Allergan, USA) injection improved BCVA, but the intra-retinal cyst persisted. One patient developed retinal detachment following a retinal tear near a retinopexy and was treated successfully with PPV and sulfur hexafluoride (20%) (34).

Conclusions

From the evidence currently available, it seems reasonable to suggest that the amniotic membrane may be transplanted instead of RPE or Bruch's membrane for the late stages of ARMD.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Sayena Jabbehdari) for the series "Novel Treatment in Age-related Macular Degeneration" published in *Annals of Eye Science*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the

Narrative Review reporting checklist. Available at https://dx.doi.org/10.21037/aes-21-17

Peer Review File: Available at https://dx.doi.org/10.21037/aes-21-17

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/aes-21-17). The series "Novel Treatment in Age-related Macular Degeneration" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aes-21-17
Cite this article as: Habibi A, Ashraf Khorasani M. Amniotic membrane as a novel treatment in age-related macular degeneration: a narrative review. Ann Eye Sci 2021;6:39.