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Review Article

Anterior lens capsule: biomechanical properties and biomedical engineering perspectives

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ABSTRACT.

Anterior lens capsule, as the thickest basement membrane in the body, has its unique physiology characteristics. In ophthalmology, many attempts have been made to culture different kinds of cells including iris pigment epithelial cells, retinal pigment epithelial cells, corneal epithelium and endothelium cells, trabecular meshwork cells etc and anterior lens capsule has been confirmed to be served as an excellent scaffold for the growth and expansion of different ocular cells. Furthermore, anterior lens capsule also has unique potential in gestation evaluation and the treatment of various ocular diseases, including corneal ulcer, glaucoma, age-related macular degeneration and macular hole, etc. Here, we provide an overview of the biomechanical properties and biomedical engineering perspectives of anterior lens capsule.

Key words: anterior lens capsule – biomedical engineering – cell cultivation

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Introduction

The lens capsule is an acellular, soft, smooth, transparent basement membrane that completely encapsulates the crystalline lens, maintaining its shape. It can act as a barrier and separate the lens from infectious viruses and bacteria. The lens capsule is generally divided into anterior capsule, posterior capsule and pericapsular membrane. Reviews of the lens capsule have been made before, but here, we mainly focus on the anterior lens capsule, especially its biomedical engineering perspectives, which were never involved previously.

To capture as much literature as possible, an initial search of PubMed, EMBASE, Web of Science and ScienceDirect with 'lens capsule [title]' was performed and papers related to our topic were extracted. When discussing the biomedical engineering perspectives, a further search of 'lens capsule and cell cultivation', 'lens capsule and cornea ulcer', 'lens capsule and trabeculectomy', 'lens capsule and macular' was performed. Relevant papers from the reference lists of our enrolled articles were manually searched for additional input. The search was restricted to articles written in English language. However, papers written in other languages with at least an English abstract was also considered.

Biomechanical properties

The detailed biomechanical properties of the lens capsule were reviewed elsewhere (Krag 1999; Krag & Andreassen 2003; Danysh & Duncan 2009; Avetisov et al. 2020). Briefly, anterior lens capsule (ALC) thickness ranges from 4 to 30 μm, which is different between the optical (1.8–24.9 μm) and histological (6.5–15.2 μm) measurements (Ziebarth et al. 2005). The anterior capsule is thicker than the posterior, and it is known to increase in thickness with age (Barraquer et al. 2006; Dong et al. 2017). By Atomic Force Microscopy (AFM), the interfibrillar spacing of human ALC was measured to be 1.08 ± 0.25 μm and the fibre diameters were 339 ± 135 nm (Sueiras et al. 2015), while in another study, the average interfibrillar spacing and fibre diameter dimensions were 0.81 ± 0.35 μm and 282 ± 111 nm, respectively (Ţălu et al. 2018). Anterior lens capsule (ALC) is primarily composed of laminin, collagen IV and sulphated glycosaminoglycans, which give it with viscosity, ductility and elasticity, thereby enabling the capsule to play accommodation function successfully by altering the shape of the lens (Ronci et al. 2011). Other components include entactin/nidogen, agrin, collagen XVIII and overall, these are the same molecules that have been found in most other basement membranes (Danysh & Duncan 2009; Avetisov et al. 2020). Anterior lens capsule (ALC) is regionally anisotropic, with the circumferential direction becoming increasingly stiffer than the meridional direction towards the equator (Pedrigi et al. 2007). The effect of age on ALC elasticity is controversial. Ageing of the human ALC is reported to

be associated with a progressive loss of mechanical strength (Krag et al. 1997) while in another study, capsular elasticity did not show a significant correlation with age (Assia et al. 1991). Fisher (1969) showed that the elastic Young's modulus of ALC steadily decreased throughout life while Ziebarth et al. (2011) found that Young's modulus of elasticity assessed by AFM, increased significantly with age. The permeability of the lens capsule to heavy-metal protein carriers was also reported to increase with age, whereas the diffusion of these carriers was not dependent on age (Sueiras et al. 2019). Van den Bogerd et al. (2018) performed collagenase degradation to evaluate ALC's resistance to degradation in vitro, and they found it took 6 and 13 hr for ALC to attain 50% digestion and complete digestion.

Biomedical engineering perspectives

Application of ALC as a cell carrier

Cultivation of human cells of any type is definitely a challenging project. Described as 'Biomedical Engineering', cultivated cells could be applied in assisting the building process of new healthy structures in the human body and creating an arsenal for numerous in vitro studies. In ophthalmology, many attempts have been made to culture different kinds of cells and several scaffolds were investigated, including native membranes (amniotic membrane, ALC, Descemet's membrane, etc), natural materials (collagen, fibrinogen, gelatin, silk fibroin, etc) and synthetic polymers (poly(lactide-co-glycolide), poly(L-lactic acid), poly(caprolactone), parylene-C, etc) (Feng et al. 2014; Navaratnam et al. 2015; White & Olabisi 2017; Nguyen et al. 2018). Human amniotic membrane has the advantage of containing growth, anti-angiogenic and anti-inflammatory factors that prevent or decrease fibrosis in the healing tissue, but it is not transparent and thin enough, and there is possible transfer of pathogen from amniotic membrane (Albert et al. 2012; Navaratnam et al. 2015). Collagen is inherently biocompatible, commercially available, cost-effective and non-toxic, but collagen can be degraded by proteases rapidly and the mechanical properties are weak due to high water content (Nguyen et al. 2018). The use of synthetic polymers allows for more control over scaffold parameters such as mechanical and transport properties and degradation characteristics (White & Olabisi 2017), however, most of synthetic polymers have limited elasticity (Feng et al. 2014) and they may induce inflammation in vivo (Tan et al. 2013). Anterior lens capsule (ALC) is ocular endogenous and optical transparent, its thinness is superior to other biomaterials, and can be easily obtained from cataract surgery or from donor eyes (Albert et al. 2012; Nguyen et al. 2018). All these advantages make ALC an excellent scaffold for the growth and expansion of different ocular cells, including iris pigment epithelial cells, retinal pigment epithelial cells, corneal epithelium and endothelium cells, trabecular meshwork cells etc.

Pigment epithelial cells

Hartmann et al. (1999) primarily cultured porcine iris pigment epithelial (IPE) cells and retinal pigment epithelial (RPE) cells on the top of porcine and human ALC in vitro, and found ALC may be suitable for growing and supporting monolayers of RPE and IPE. Especially IPE formed stable monolayers on ALC and could be transferred to secondary culture flasks without inflicting damage on the cells. Nicolini et al. (2000) seeded porcine RPE cells on bovine corneal extracellular matrix (ECM), isolated bovine- and porcine ALC, and tissue culture plastic in vitro, and found that RPE cells grown on porcine ALC and on ECM obtained better morphology and higher final cell density than cells grown on plastic and on bovine ALC. The cultivation of human RPE cells on ALC was also studied. Singh et al. (2001) firstly reported successful human RPE culture on ALC in vitro. After that, human RPE cell line, ARPE-19 cells, were found a more differentiated phenotype when cultured on porcine ALC than on porous polyester filters (Turowski et al. 2004). Culture of ARPE-19 cells on porcine ALC also resulted in expression of a specific set of transcripts encoding protein products that may affect epithelial differentiation, polarity and survival (Turowski et al. 2004). Lee et al. (2007) investigated human ALC as a replacement for Bruch's membrane and also explored the ideal seeding methods of ARPE-19 cells in vitro, and found that a dual-layer transplant, with RPE cells organized by centrifugation onto ALC, appeared promising in achieving native retinal function. Microcontact printing, a modern materials fabrication technique, was also confirmed to successfully control the organization of ARPE-19 cells or rabbit iris pigment epithelial cells cultured onto the human ALC surface (Lee et al. 2002). All these results indicated the potential treatment role of ALC in age-related macular disease, because transplantation of pigment epithelial cells appears to be a logical approach to replace RPE lost in the course of age-related macular degeneration (AMD).

Corneal epithelial cell

Galal et al. (2007) used human ALC as a scaffold for ex vivo growth of cornea epithelial cells, both as autologous and allogeneic. They found comparable cell growth rate, cell density and similar cell viability and vitality in the study and control groups. In another ex vivo study, it has been shown that cornea limbal epithelial stem cells could be consistently expanded on human ALC using a medium containing human serum as the only growth supplement. Cells isolated and cultivated in such an animal material-free medium were viable, preserved their pluripotency and had the directional differentiating potential into corneal epithelium *in situ* (Albert et al. 2012). These findings demonstrated that ALC can serve as an excellent scaffold for the growth and expansion of limbal epithelial cells, possibly providing a substrate for ocular surface reconstruction.

Corneal endothelial cell

Yoeruek et al. (2009) seeded human corneal endothelial cells (HCECs) on deepithelialized human ALC. After 7 days in cultivation and confluence, the HCECs formed a continuous viable monolayer with a high cell density, which were similar to native corneal endothelial cells with intact functions. In another ex vivo study, cell-scaffold interaction was assessed by measuring focal adhesions surface on ALC and plastic and primary corneal endothelial cells were grown on ALC isolated from donor eyes. They found the surface area of focal adhesions for cells grown on coated ALC was at least double that compared with other conditions,

whereas tight junctions, ion pumps and hexagonal morphology were well maintained when endothelial cells were cultured on ALC (Van den Bogerd et al. 2018). All these results recommend that ALC is an excellent scaffold for ex vivo expansion of HCECs and can be considered a suitable substrate for ocular tissue engineering and for therapy of isolated corneal endothelium diseases. Kopsachilis et al. (2012) also confirmed the successful expansion of HCECs on denuded donor eye ALC. They suggested that ALC would be better to be obtained from the lens of donor eye, because it is large enough for its potential use in future Descemet's membrane endothelial keratoplasty (DMEK) surgery, a surgery procedure that can make a quicker and safer visual rehabilitation than traditional penetrating keratoplasty. In an in vitro DMEK surgery study, the authors showed human ALC was the most suitable carrier for cultivated porcine corneal endothelial cells with good intraoperative graft handling (Spinozzi et al. 2019). In their another in vitro DMEK surgery study, HCEC-human ALC constructs also behaved most similarly to a DMEK-graft during implantation and unfolding, showing good adhesion to bare stroma (Spinozzi et al. 2020). Although further studies should be made to determine whether the HCEC-ALC complexes can maintain stromal dehydration and corneal transparency, these new bioengineered tissues may eventually offer an exciting alternative in corneal surgery. However, there is limited information about in vivo testing of the surgical handling and the therapeutic potential of tissue-engineered endothelial cell carrier constructs at present. Telinius et al. (2020) tested the feasibility of implanting human ALC with porcine corneal endothelial cells in vivo in Göttingen Minipigs, and they found the minipig was not suitable for corneal transplantation studies in vivo because of intraoperative challenges and development of retrocorneal membrane postoperatively. Further studies are required to explore other animal models.

Trabecular meshwork cell

Kopsachilis et al. (2013) proposed for the first time that ALC could be a suitable substrate for cultivation, expansion and proliferation of human trabecular meshwork (HTM) cells. In their ex vivo study, after seeding HTM cells on human ALC and examining HTM cells' morphology and viability, they found the HTM-ALC complexes exhibited cellular morphology similar to the in situ observed cells. The cultured HTM cells could be used to investigate the biological properties of HTM, accomplish experiments regarding toxic effects of various factors on HTM, and therefore, these innovative bioengineered tissues have the potential to expand the existing knowledge about glaucoma pathophysiology and develop novel therapeutic strategies regarding the management of glaucoma.

Application of the bare ALC

Besides ALC's excellent scaffold role in the growth and expansion of different ocular cells, the bare ALC also has unique potential in gestation evaluation and the treatment of various ocular diseases.

Application of ALC in evaluating gestation

Low birth weight is an important public health problem in developing countries. These at-risk babies may not receive simple, low-cost treatments that could save lives without accurate gestational age (GA). However, accurate GA assessment in developing countries is often compounded by the inaccuracies of last menstrual period dating and the infrequency or nonavailability of prenatal ultrasound. Therefore, alternative method such as the anterior lens capsule vascularity (ALCV) evaluation has been applied in such cases.

Hittner et al. (1977) categorized ALCV between the 27th and the 34th weeks of gestation into 4 grades: Grade I: few thin vessels in the periphery; Grade II: more clearing with thinning of peripheral vessels; Grade III: early vascular atrophy with central clearing; Grade IV: ALCV covers entire anterior lens surface. These grades corresponded to 33–34, 31–32, 29–30 and 27–28 weeks of gestation respectively. Before the 27th week, the cornea is too opaque to permit good visualization of ALCV whereas after the 34th week, the ALC vessels are usually resorbed completely.

Nagpal et al. (2004) enrolled 139 neonates of 27–40 weeks gestation (60 appropriate for gestational age (AGA) and 79 small for gestational age (SGA)) to assess clinical gestational age and ALCV grading within 24 hr of birth. They found a good correlation between ALCV grading and clinical estimates of gestation age in AGA neonates, which is consistent with earlier studies (Hittner et al. 1977; Sasivimolkul et al. 1986). However, for SGA neonates, the correlation is weaker and the regression appears to continue up to 39–40 weeks, indicating that ALCV grading could under-estimate the gestation of SGA subjects by an average of 3 weeks compared to AGA neonates (Hittner et al. 1981). Recently, Patel et al. (2019) found that smartphone ophthalmoscopy and semiautomated image analysis can quantify ALCV features and estimate GA among preterm neonates with a high level of agreement with ultrasound estimated gestation age, providing a novel, rapid, accurate and noninvasive technology to objectively estimate postnatal GA in preterm neonates, especially in areas where GA might not be known at birth.

Application of ALC in corneal ulcer

Corneal ulcer, a defect of the corneal epithelium involving the underlying basement membrane (BM) and stroma, is a potentially vision-threatening ocular emergency. Several complications, including corneal scarring or perforation, cataract, glaucoma, anterior or posterior synechiae, uveitis, endophthalmitis and vision loss, can occur from corneal ulcer. Therefore, an urgent or emergent ophthalmologic evaluation and prompt treatment is often needed. At present, multiple medical treatment and surgical strategies have been used to treat corneal ulcer, such as proper antimicrobials, corneal gluing, amniotic membrane transplantation, conjunctival flap transplantation and keratoplasty (Stamate et al. 2019).

Anterior lens capsule (ALC), as the thickest BM of the body, has been transplanted to promote epithelial growth of corneal ulcer. Kozak et al. (2004b) created mechanical corneal ulcer model in rabbit eyes with a 6-mm corneal trephine and sutured ALC (from a healthy donor rabbit) into the ulcer bed. During the 6-month follow-up period, the treated eyes were found to reepithelialize faster than the control group eyes and have a lower corneal

opacification percentage. Histopathology showed normal epithelium overlying the transplanted ALC and no inflammatory cells infiltration in the subepithelial stroma and the following immunofluorescent analysis revealed no rejection reaction and no participation of humoural immunity in immune reaction Kozak et al. (2004a). Their further ultrastructural study by electron microscopy indicated that the faster healing from ALC allotransplantation might be resulted from the continuously formed epithelial BM and numerous hemidesmosomes (Kozak et al. 2003).

Although there is no clinical data, the above animal model results are exciting and encouraging. If ALC transplantation is successful in humans, it could help replace or restore Bowman's layer and perhaps epithelial BM in nonhealing ulcers and provide an alternative to treat persistent epithelial defects with chronic corneal ulcers.

Application of ALC in glaucoma

Glaucoma, characterized by optic nerve atrophy and visual field defects, is a severe, potentially blinding disease that affects all age groups and all populations. Although the aetiology of glaucoma is not very clear yet, controlling the intraocular pressure (IOP) at an early stage has been evidenced to slow down or stop glaucoma progression. Trabeculectomy, introduced by Cairns in 1968, remains the gold standard of external filtering surgery for many glaucoma cases. Surgery failure is mainly owing to the postoperative fibrosis at the filtering site, including the sclera flap level and/or conjunctiva-Tenon's capsule-episcleral interface. In order to improve success rate, antimetabolites primarily mitomycin-C (MMC) and 5-fluorouracil (5-FU) have been introduced in trabeculectomy. However, the application of antimetabolites also increases the risk of bleb leakage, toxic epitheliopathy, prolonged hypotony, blebitis or even endophthalmitis (Collignon-Brach 1993; Smith et al. 1994; Chen et al. 2018). Many foreign biomaterials, such as horse hair, silk threads, nylon, gelatin, amniotic membrane and silicone tubes, have also been implanted in glaucoma surgery to aid filtration, but availability issues and cost factors exist.

Anterior lens capsule (ALC) was first introduced in glaucoma surgery in 1997. Anwar et al. (1997) put ALC flap under the sclera flap in 25 eyes during their combined trabeculectomy and extracapsular cataract extraction procedure and found the capsular wick could help maintain glaucoma filtration. In our randomized comparative study (Lu et al. 2009), use of ALC in 29 eyes was compared against 21 eyes in MMC group. During phacotrabeculectomy, ALC was obtained by continuous curvilinear capsulorhexis, the lens epithelial cells were scraped off carefully with a lenticular hook, the ALC was then washed twice with balanced salt solution and was finally placed under the scleral flap and sutured (Fig. 1). Our results showed no statistical difference between the ALC group and the MMC group in the formation of functional filtering blebs, IOP, the number of antiglaucoma medications and best corrected visual acuity during our 12-month follow-up. At 1 month after surgery, ALC could be detected by ultrasound biomicroscopy (UBM) in the filtering site (Fig. 1) and no rejection reaction or ALC-related complications were noted during the whole follow-up period. However, at 3 months after surgery, the ALC could not be detected by UBM any more (unpublished data). Therefore, we infer the biodegradation of ALC in vivo may occur between 1 and 3 months. Besides our study, several other studies also confirmed the efficacy and safety of ALC transplantation in phacotrabeculectomy (Emarah & El-Helw 2011; Das et al. 2018) or phacoemulsification-deep sclerectomy (Rekas et al. 2010) thereafter.

Several factors can contribute to the encouraging clinical outcome of ALC transplantation. First, ALC can aid filtration by draining the aqueous humour to the subconjunctival space by capillary action. Second, as an avascular basement membrane, ALC can mechanically isolate the scleral flap and the scleral bed to prevent adhesions of the scleral flap to the fascial capsular fibres, thus maintain the smoothness of the sclerotomy site and keep an effective filtration space. Third, ALC derives from the ectoderm and sclera from mesoderm, tissues from different blastoderms do not adhere with each other. Fourth, ALC is inert, nonimmunogenic or allergenic, and it will not lead to rejection reaction. Moreover, the potential antiangiogenetic and anti-proliferation effects of ALC could be an additional mechanism of action (Anwar et al. 1997; Lu et al. 2009).

Anterior lens capsule (ALC) is universally available in every combined surgery, obviating the need to obtain additional materials and reducing cost for the patients. The application of ALC requires no additional handing or processing cost, no storage or sterilization concerns, and can be an ideal alternative antifibrotic treatment for glaucoma. The good visual rehabilitation and successful IOP reduction and the absence of significant complications from the existing study results can yield more widespread application of ALC in combined glaucoma and cataract surgery.

Application of ALC in AMD

Age-related macular degeneration (AMD), as the leading cause of blindness in industrialized nations, is characterized by retinal pigment epithelial

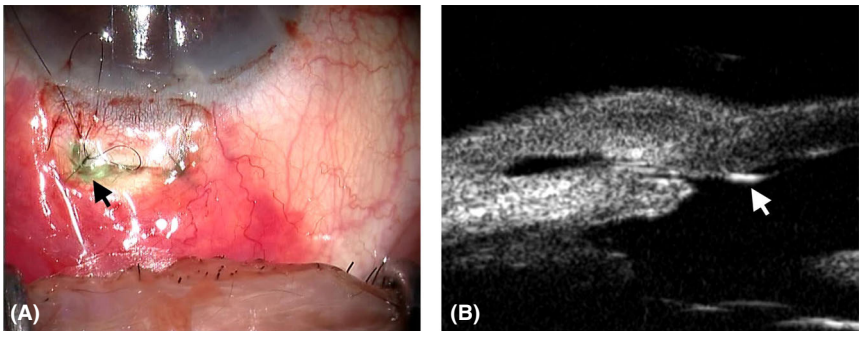

Fig. 1. In vivo application of anterior lens capsule (ALC) in glaucoma. (A) Snapshot during phacotrabeculectomy. Anterior lens capsule (ALC) was put and sutured under the scleral flap (black arrow; ALC was stained by indocyanine green for better visualization). (B) Ultrasound biomicroscopy (UBM) image after surgery. At 1 month after surgery, ALC could be detected by UBM in the filtering site (white arrow).

(RPE) cells loss and in some cases, choroidal neovascularization (CNV) formation (Zarbin 1998). Although there are some treatments to destroy the new blood vessels, there is no evidenced therapy to restore RPE cells or the overlying retina for AMD. Replacement of the dysfunctional RPE cells with healthy ones may provide a potential treatment for AMD, but the transplanted RPE may not adhere well to abnormal Bruch's membrane (Castellarin et al. 1998; Del Priore & Tezel 1998). Therefore, it has been proposed that replacing the basement membrane along with RPE cells may contribute to a successful transplant for AMD and it is necessary to find a biocompatible substrate replacing abnormal basement membrane (Binder et al. 2007; Wang et al. 2010).

As having the similar composition with Bruch's membrane such as collagen IV, proteoglycan and fibronectin and its inherent biocompatibility, ALC can act as a permanent barrier to prevent CNV and can be a potential autologous implant to circumvent the immune response. Nicolini et al. (2000) transplanted the porcine ALC with confluent porcine RPE cells to the subretinal space (SRS) in Danish domestic pig in vivo and found the ALC was well tolerated in SRS within two weeks of observation. Kiilgaard et al transplanted porcine ALC to SRS of 20 eyes from 19 young Danish landrace pigs, and demonstrated that ALC was well tolerated in SRS without inflammation and was covered with well-differentiated monolayers of PRE cells, if Bruch's membrane was left intact (Nicolini et al. 2000; Kiilgaard et al. 2002). Additionally, it was also reported that ALC is a good substrate for RPE cells growth (Hartmann et al. 1999). Moreover, ALC was proven to have comparable permeability with

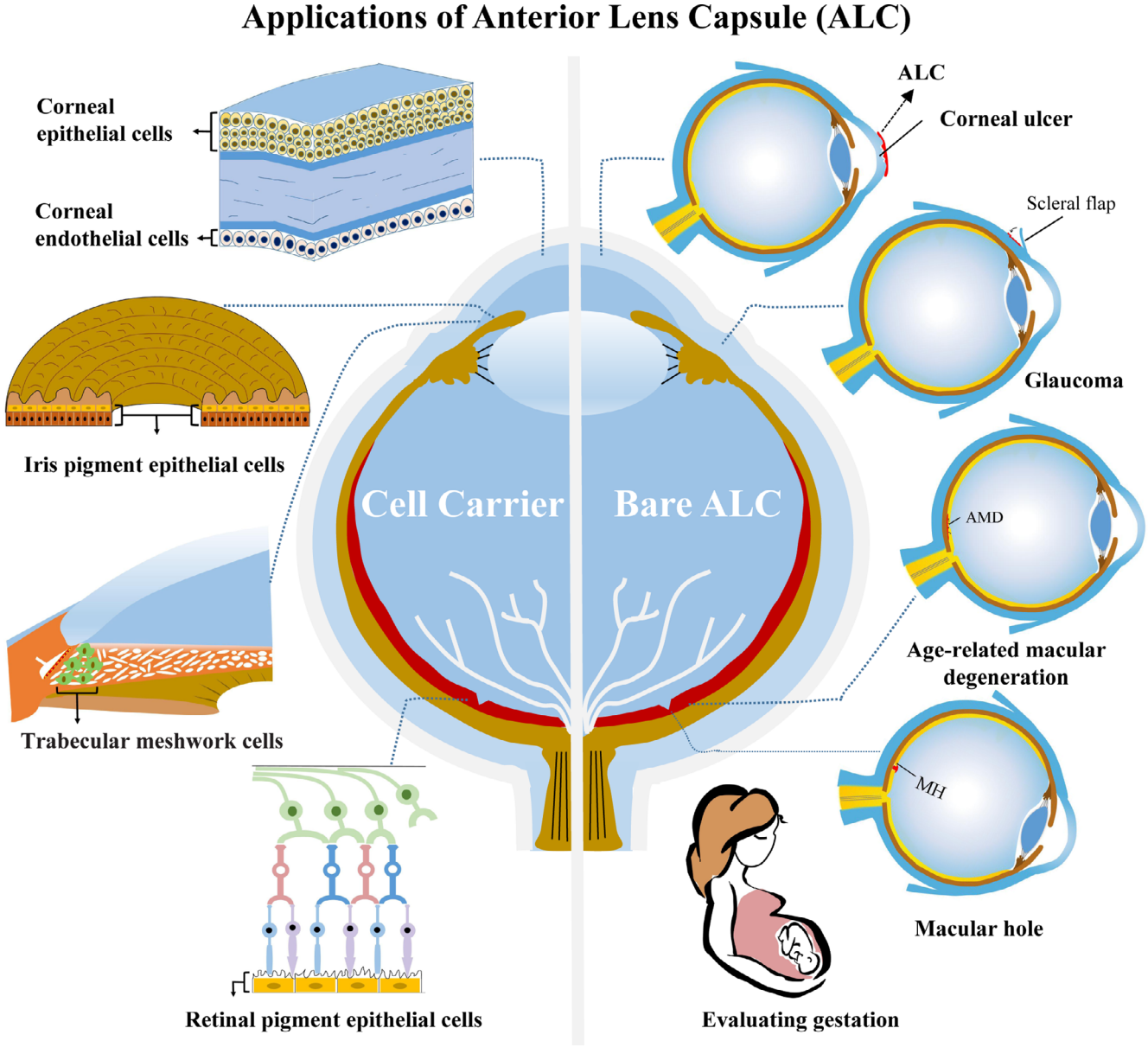

Fig. 2. Schematic summary of application of ALC as a cell carrier or bare ALC. Anterior lens capsule (ALC) can be served as an excellent scaffold for the growth and expansion of different ocular cells. Anterior lens capsule (ALC) also has unique potential in gestation evaluation and the treatment of various ocular diseases, including corneal ulcer, glaucoma, age-related macular degeneration and macular hole, etc.

Bruch's membrane, enabling ALC similar diffusive properties to nutrients to support the overlying RPE (Lee et al. 2006). All of these properties indicate that ALC is a promising replacement tissue for Bruch's membrane as a potential treatment for AMD.

Application of ALC in macular hole

A macular hole (MH) is a full-thickness neuroretinal defect or break of the fovea, most of which are considered idiopathic. The standard therapeutic regimen for full-thickness MH includes pars plana vitrectomy combined with internal limiting membrane (ILM) peeling, and air or gas tamponade. However, quite a proportion of the MHs did not achieve complete closure. Internal limiting membrane (ILM) free flap insertion into the hole has been advocated to facilitate hole closure in refractory cases (Morizane et al. 2014). However, it is very difficult to peel the peripheral ILM in cases whose ILM had already been peeled within the arcade in previous surgeries or when only shreds of ILM can be obtained. Furthermore, the ILM flap tends to lost easily during manipulation because ILM fragments tend to float into the vitreous cavity.

In order to improve the hole closure rate in refractory MH cases, Chen & Yang (2016) transplanted autologous ALC or posterior lens capsule into the MH in 20 eyes with persistent MH after previous standard MH surgery. The results showed that the hole was closed in all the 10 eyes with ALC transplantation and visual acuity was improved in most cases. Hole closure was also reported to be achieved in two chronic MH cases by ALC flaps injection into the hole without ILM peeling (Yepez et al. 2018), which is different from the surgery procedure of Chen et al. Peng et al. (2018) evaluated the efficacy of ALC transplantation and autologous whole blood application in ten refractory MH cases. Lens capsule flap was acquired from the same eye in eight cases and the fellow eye was used in two aphakic eyes without sufficient lens capsule. After surgery, the MH was completely closed in nine eyes and partially closed in one eye. The encouraging results are believed to be resulted from several properties of ALC: (1) fibronectin, released from lens epithelial cells, may play a role in lens wound healing and posterior capsule opacification as a cell signalling molecule; (2) ALC is considered a reservoir for growth factors that contribute to lens development. Matrix metalloproteinases combined with inhibitors of metalloproteinases regulate growth factors releasing from BM and take part in BM remodelling; (3) the integrated collagen IV network within the laminin scaffold can provide the required strength and stability and contribute to the perifoveal cysts absorption (Danysh & Duncan 2009; Yepez et al. 2018).

Although the transparent nature of ALC makes it difficult to be seen clearly and necessitates the vital dye staining during surgery, which poses potential retinal toxicity, an ALC flap can settle down on the retinal surface and be directed to the designated place easily because of its higher density than ILM free flap. Additionally, ALC flap can be obtained more easily than ILM free flap, making its popular use in the future possible (Chen & Yang 2016).

The applications of ALC as a cell carrier or bare ALC are summarized in Fig. 2.

Conclusion

Anterior lens capsule (ALC), as the thickest basement membrane in the body, can be served as an excellent scaffold for the growth and expansion of different ocular cells, such as retinal pigment epithelial cell, corneal epithelium and endothelium cell and trabecular meshwork cell, etc. It also presents potential biomedical engineering application in the treatment of several ocular diseases, including corneal ulcer, glaucoma and macular diseases, etc. Anterior lens capsule (ALC) can be easily collected during cataract surgery, hence providing a rich source of a biologic membrane sheet that can act as a scaffold for cultivation. Furthermore, ALC can be obtained from the same patient as an autologous biologic substrate, minimizing the risk of immune reaction and biotoxicity. All these properties of ALC make the increasing and widespread use of ALC reasonable and promising in the future.

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