SciMedCentral

JSM Biotechnology & Biomedical Engineering

Review Article

Recent Strategies of Therapeutic Cell Delivery for Regeneration of Corneal Endothelium

Hyeongmin Kim[1,2,3], Young Joo Shin[4] and Jaehwi Lee[1,2,3]*

[1]*Department of Pharmacy, Chung-Ang University, South Korea*
[2]*Bio-Integration Research Center for Nutra-Pharmaceutical Epigenetics, Chung-Ang University, South Korea*
[3]*Center for Metareceptome Research, College of Pharmacy, Chung-Ang University, South Korea*
[4]*Department of Ophthalmology, Hallym University College of Medicine, Republic of Korea*

***Corresponding author**
Jaehwi Lee, Department of Pharmacy, Chung-Ang University, 84 Heuksuk-ro, Dongjak-gu, Seoul 06974, Republic of Korea, Tel: 8228205606; Fax: 82 28167338; E-mail: jaehwi@cau.ac.kr

Submitted: 02 March 2016
Accepted: 15 April 2016
Published: 18 April 2016
ISSN: 2333-7117

Keywords
- Corneal endothelium
- Cell transplantation
- Regenerative medicine
- Tissue engineering
- Magnetic cell delivery

Abstract

Cell-based therapies have been increasingly explored as a potential alternative treatment method of corneal endothelial dysfunction. Up to date, researchers have mainly dedicated enormous efforts to establishing fundamental techniques for culture and characterization of human corneal endothelial cells (HCECs) and human corneal endothelial progenitor cells (HCEPCs). However, in terms of cell delivery methods, existing approaches have shown many limitations such as low cell delivery efficiency, intricate processes, and inevitable damages on the cornea occurring during surgical procedure. The problems related to cell delivery to the eye have significantly hindered translation of the novel cell-based therapeutic systems into clinical practice. Thus, importance of developing novel strategies for cell delivery to the corneal endothelium has been increasingly growing. In this context, this review will discuss key approaches investigated until recently for efficient cell delivery to the corneal endothelium along with future perspectives on a need of developing cell delivery systems for treatment of corneal endothelial dysfunction.

ABBREVIATIONS

HCEC: Human Corneal Endothelial Cell; **HCEPC:** Human Corneal Endothelial Progenitor Cell; **SPION:** Superparamagnetic Iron Oxide Nanoparticle

INTRODUCTION

The cornea is a transparent a vascular tissue constituting the fore outer part of the eye and largely responsible for its refractive capacity together with the lens and anterior chamber [1]. The cornea consists of three different layers (corneal epithelium, stroma, and endothelium) along with two acellular membranes (Bowman's layer and Descemet's membrane) located between the layers. The corneal epithelium, the outermost layer of the cornea, refracts light and protects the eye from external environments. The corneal stroma is a transparent tissue composed of extracellular matrix with sparsely distributed keratocytes and contributes to maintaining the shape and structural integrity of the cornea. The transparency of the stroma is retained by the corneal endothelium, the innermost layer of the cornea.

The corneal endothelium is a monolayer of the human corneal endothelial cells (HCECs) with polygonal morphologies. This tissue plays a pivotal role in maintaining a dynamic balance of fluid, nutrients and salts between the corneal stroma and aqueous humor. The tight junction-based diffusive barriers and active transporters of the corneal endothelium allow fluid and its solutes to pass into the stroma and draw excess fluid and waste products out to the aqueous humor [2–4]. This function of the corneal endothelium relies largely on quantity and quality of HCECs. On average, cell density of adult corneal endothelium is 2,400 cells/mm^2, ranging from 1,500 to 3,500 cells/mm^2 [5]. However, the density of the cells decreases with aging at a speed of 0.5% decrease per year [6]. In addition, in contrast to the corneal epithelial cells with highly proliferative potential, HCECs have a very limited proliferation capacity because the cell cycle of most of the cells is arrested in the G1 phase [7]. Therefore, a reduction of cell density of the corneal endothelium caused by aging, trauma, and/or disease is potentially irreversible. Although HCECs can extend themselves and migrate toward an

area devoid of the cells to compensate for the loss of the cell density, accumulated damages on the corneal endothelium can eventually lead to functional failure [1]. In this case, the corneal stroma swells by edema, followed by collapse of the corneal epithelial layer and loss of vision [8,9].

Currently, the only available treatment method for corneal blindness caused by corneal endothelial dysfunction is corneal transplantation. However, availability of donor corneas required for the corneal transplantation is extremely limited worldwide [10]. Moreover, the donor corneas should meet very strict criteria, and the therapeutic outcomes can be lowered by complications such as immune rejections [11,12]. The high cost and needs for well-equipped surgical facilities and highly trained specialists also limit the access to the corneal transplantation. In this context, new therapeutic modalities for treatment of corneal endothelial dysfunction are highly needed.

For the past decades, enormous efforts have been made to develop a novel cell-based treatment method for regeneration of the depopulated corneal endothelium. The concept of this new therapeutic modality is that delivering and replenishing HCECs or progenitor cells that can be differentiated to HCECs to the compromised corneal endothelium. Up to date, researchers have mainly focused on establishing fundamental techniques for cell culture and characterization. As a result, HCECs, exhibiting very limited proliferative capacity in vivo, now can be readily cultured in vitro using well-designed culture media [13,14]. Corneal endothelial progenitor cells, existing in the peripheral region of the cornea with comparatively low numbers, can also be effectively isolated using a sphere-forming assay [15,16]. In addition, the cells can be multifacetedly characterized using various physical and biochemical methods [17-19]. However, in terms of cell delivery technologies to the depopulated corneal endothelium, significant advances have not been achieved yet. Existing cell delivery methods have shown many disadvantages such as low cell delivery efficiency and intricate procedures, limiting therapeutic efficacy of HCECs and the progenitor cells. Addressing the problems related to cell delivery, thus, is currently very critical for translation of the novel cell-based therapeutic modality into clinical practice. Therefore, in this review, approaches investigated until recently for efficient delivery of corneal endothelial cells will be discussed along with future perspectives based on a need of developing cell delivery systems for the treatment of corneal endothelial dysfunction.

Simple cell injection to the anterior chamber

Cell injection methods have typically been used for delivery of HCECs or corneal endothelial progenitor cells to the corneal endothelium due to their advantages such as simple procedure and minimal invasiveness compared to surgery. The process of the method is generally initiated by injecting HCECs or corneal endothelial progenitor cells suspended in appropriate media into the anterior chamber. Based on literature survey this approach has only been applied to animals such as rabbits and monkeys. The animals are anesthetized and usually made to keep a prone position so as to guide the injected cells toward the corneal endothelium. As time progresses, the cells reach the corneal endothelium, then are expected to attach and to be integrated into the tissue.

For example, Mimura et al. demonstrated regenerative effect of human corneal endothelial progenitor cells (HCEPCs) in a rabbit model with corneal endothelium deficiency using a cell injection method. They isolated and obtained HCECs and HCEPCs from a cornea of the human donor. As for HCEPCs, the cells were isolated as a form of spheres using a sphere-forming assay, which has widely been used to separate adult stem cells or progenitor cells [15]. The two types of cells were injected into the anterior chamber of the rabbit eye, and the rabbits were kept in an eye-down position to make the injected cells move toward the posterior cornea surface for 24 hours under deep anesthesia. As a result, corneal edema present in the rabbits, which was caused by corneal endothelial deficiency, was restored and their corneal thickness also decreased to a normal level. However, these effects were not clearly observed from the rabbits injected with HCECs. The reason for this might be due to higher proliferative capacity of HCEPCs in vivo than that of HCECs [16,20,21]. Thus, the cell injection approach can be potentially used as a simple method to deliver the therapeutic cells to the depopulated corneal endothelium. However, for patients, keeping the eye-down position for long time would be very burdensome. In this regard, another study was performed to determine the minimal time necessary for the depopulated corneal endothelium to be recovered in the same experimental condition [22]. The authors demonstrated that the time taken for treatment of corneal endothelial dysfunction could be reduced from 24 hours to 6 hours. However, maintaining the eye-down position for 6 hours would still be hard to patients with corneal endothelial deficiency.

There are great risks that the cells injected into the anterior chamber would move toward unwanted area of the eye such as the trabecular meshwork and surface of the iris, thereby increasing intraocular pressure or degenerating the iris [23]. Low efficiency of the cell attachment to the corneal endothelial surface caused by lack of controllability of the cell movement could also be problematic. Combining together, although the cell injection method has widely been used for the delivery of HCECs and HCEPCs to the compromised corneal endothelium, it has still many disadvantages that should be overcome for clinical translation.

Transplantation of engineered corneal endothelium with supporting materials

Besides the cell injection method, tissue engineering technique-based approaches have also been used to transplant HCECs to the depopulated corneal endothelium [24-26].The basic concept of this method is engineering an artificial corneal endothelium with HCECs cultured in vitro and transplanting it to the posterior cornea surface along with supporting materials. In general, HCECs are isolated from donor corneas and cultured in vitro, and the cultured cells are seeded on supporting materials, followed by culturing the seeded cells to be confluent [27,28]. Then, the cell monolayer with an appropriate cell density with the supporting materials is transplanted to the posterior side of the cornea using a surgical method.

One of the most critical criteria that should be met for successful regeneration of the corneal endothelium by the tissue engineering method is establishing a suitable supporting material with necessary properties. The supporting materials should reinforce the mechanical weakness of the engineered

Table 1: Advantages and disadvantages of each cell delivery method for treatment of corneal endothelial dysfunction.

Method	Advantages	Disadvantages
Simple cell injection into the anterior chamber	• Simple procedure of transplanting HCECs to the corneal endothelium • Minimal invasiveness	• Low cell delivery efficiency • High possibility of occurrence of adverse effects caused by cell movement to unwanted area • Inconvenience for patients due to a need of keeping an eye-down position for long time
Transplantation of engineered corneal endothelium	• Better maintenance of HCEC functions due to strong interactions between the cells • Well-organized tissue structure of engineered corneal endothelium similar to that of human corneal endothelium	• Difficulty of handling engineered corneal endothelium with thin and physically delicate properties • Damages on the cornea happening during surgical procedure • Necessity of post-operative recovery time and visual rehabilitation
Magnetic force-guided cell delivery	• High cell delivery efficiency • Low possibility of occurrence of adverse effects caused by cell movement to unwanted area • Minimal invasiveness	• Possible toxicity of magnetic particles endocytosed in HCECs on the cells and surrounding tissues • Difficulties in optimizing experimental conditions affecting cell movement injected into the anterior chamber

Abbreviations: HCECs: Human Corneal Endothelial Cells

corneal endothelium, which possibly makes handling of the engineered tissue difficult during transplantation procedure [29]. In addition, they have to offer appropriate microenvironment for the maintenance of various cellular activities of HCECs such as cell adhesion and proliferation [30]. The supporting materials also have to allow diffusion of nutrients and gases between the corneal stroma and aqueous humor, and should be biocompatible, biodegradable, and transparent. In this regard, supporting materials should preferably possess similar biological, physiological, and mechanical properties to those of Descemet's membrane, the base membrane of the corneal endothelium.

Up to date, numerous substances have been explored as potential supporting materials for engineering and transplanting the artificial corneal endothelium. The substances can largely be categorized as biological, synthetic, and composite materials. The biological materials include human-derived tissues such as amniotic membrane [27,31] and decellularized corneal tissues [32-35] and natural polymers like collagen [36], gelatin [37], fibronectin [38], and laminin [39]. Amniotic membrane has been used as a supporting material due to its anti-inflammatory and non-immunogenic properties [40,41]. However, it has limitations such as donor dependency, inter-donor and intra-donor variations, semi-opaque property, and possible contaminations of pathogens [29]. The decellularized corneal tissues are promising as a supporting material because they have similar shape, mechanical strength, and transparency to those of real human cornea. They have also biological properties that can promote the expression of function-related proteins in the engineered corneal endothelium. Many literatures have demonstrated that the decellularized corneal tissues could recover corneal endothelial dysfunction when transplanted to the posterior corneal surface of animal models along with the engineered corneal endothelium [42-45]. The decellularized tissues, however, have same limitations to those of amniotic membrane such as donor dependency and possible contamination [29]. Natural polymers constituting the extracellular matrix such as collagen and fibronectin have shown promise as a supporting material due to their diverse bioactive moieties that can retain essential cellular activities of HCECs [33,36,37,46,47]. However, they have often exhibited different results in terms of adhesion, proliferation, and phenotype of HCECs, and therefore further studies are required to achieve the consistency of the cellular reactions caused by the natural polymers.

Synthetic polymers have distinctive advantages compared to biological materials such as high purity with fully defined chemical composition, controllable mechanical and biodegradable properties, and low risk of contamination. Thus, one can fabricate supporting materials with well-designed features for transplantation of engineered corneal endothelium. However, synthetic polymers generally lack of biological properties needed to maintain the cellular activities of HCECs. For this reason, researchers have used composite material-based supporting materials, thereby maximizing the advantages of each material. For example, Wang et al. investigated chitosan-polycaprolactone blends as a portential carrier for corneal endothelial transplantation [48]. Chitosan is a biomaterial with good biocompatibility, biodegradability, and some biological properties similar to those of glycosaminoglycan-rich extracellular matrix and polycaprolactone is a synthetic polymer that can provide adequate mechanical properties to the carrier. The chitosan-polycaprolactone blends exhibited good physical properties including appropriate mechanical strength and transparency, and corneal endothelial cells could be cultured on the substrate and reach confluence. In addition, the corneal endothelial cells considerably expressed tight junction and extracellular matrix proteins when seeded on the substrate. In another study, hydroxyl chitosan, gelatin and chondroitin sulfate were compositely used to prepare a carrier for transplantation of the engineered corneal endothelium [49]. The carrier demonstrated good transparency, permeability, biodegradability, and mechanical properties. Furthermore, corneal endothelial cells could be well attached on the carrier and proliferated better than those cultured on a control substrate composed of polystyrene.

However, this tissue engineering approaches have also showed significant disadvantages. The engineered corneal endothelium is very thin and delicate, and it is therefore technically

challenging to transplant the engineered tissue to the posterior corneal surface [50]. Although various supporting materials have been used to address this problem as described above, handling the monolayer of HCECs attached to the supporting materials is still regarded to be considerably difficult [50]. The transplanted cell sheets could also be displaced from the host's cornea due to lack of strong interaction between the cell sheet and the host's cornea [46]. Moreover, surgical procedures performed during the transplantation process can result in unwanted damages on the cornea, thereby causing unexpected changes of corneal refractive property and requiring post-operative recovery time and visual rehabilitation [30,51,52]. In terms of the supporting materials, they should possess a set of requisite properties such as transparency, permeability to physiological components, proper curvature, flexibility, biodegradability, biocompatibility, and proper mechanical strength for successful therapeutic outcomes, but fulfilling all of the requirements at the same time is extremely challenging [28,53]. To the best of our knowledge, none of supporting materials well-designed and fully characterized according to aforementioned criteria has been reported yet. Thus, as with the cell injection method, the tissue engineering approaches also have a lot of drawbacks limiting their applicability in clinical practice.

Magnetic field-guided cell delivery to the corneal endothelium

In order to overcome the disadvantages of the simple cell injection method aforementioned, researchers have tried to conflate the concept of magnetic force-assisted cell delivery following cell injection to the eye. This concept hypothesized that iron particles embedded in corneal endothelial cells could be more efficiently delivered to the posterior corneal surface by externally applied attractive force of magnets [54]. Indeed, Mimura et al. demonstrated that iron-endocytosed corneal endothelial cells could more effectively recover symptoms caused by corneal endothelial dysfunction than the cells devoid of iron particles [54]. However, the ferromagnetic (iron) particles and even the cells incorporating them used in this study could possibly be self-aggregated because magnetic properties of the particles were retained after eliminating the magnets [55,56]. This phenomenon can lead to unwanted increase in intraocular pressure and decline of the cell localization capacity [57].

In order to address this problem related to the ferromagnetic particles, Patel et al. alternatively used superparamagnetic nanoparticles (SPIONs), known to lose magnetic properties after removal of an external magnetic field ,for transplantation of HCECs [57].They incorporated SPIONs within HCECs and performed an in vitro cell delivery experiment using a human eye anterior segment perfusion model under an external magnetic field. As a result, SPION-endocytosed HCECs could be efficiently delivered to the posterior region of the cornea, and they formed flat, single cell layers associated with collagen fibrils of the human anterior segment. However, in this study, experimental variables were not optimized such as the number of transplanted HCECs, the intensity and duration of external magnetic field, the strength and shape of magnets, and the distance between the magnets and the cornea. Optimization of such variables would be very critical for achieving appropriate cell attachment to the posterior corneal surface, required cell density of the corneal endothelium, and uniformity of the cell density over the whole tissue.

Moysidis et al .have recently conducted a study on magnetic field-guided delivery of HCECs in vitro model with improved experimental conditions [58]. They controlled a range of parameters affecting the cell movement by magnetic force such as intensity and distribution of magnetic field, magnet shape and positioning, and concentration of SPIONs incorporated in HCECs. As a result, they demonstrated a positive logarithmic relationship between magnetic field strength and density of HCECs delivered on the posterior surface of contact lenses, which was used as an in vitro model mimicking the human cornea. Furthermore, their findings might imply that movement of HCECs could be controlled in different directions by varying distribution of magnetic field applied. Thus, the magnetic cell delivery approach can be more powerful by regulating key parameters that significantly influence the fate of cells injected into the anterior chamber.

However, in spite of the advantages of the magnetic cell delivery strategy, safety concerns of magnetic particles have also been raised. The iron particles endocytosed in HCECs can leak from the cells by some mechanisms such as exocytosis and lysosomal degradation [59], and possibly cause corneal hemosiderosis and damages on surrounding tissues such as the retina and choroid [54]. Although a study on long-term evaluation of the safety of iron particles in the rabbit anterior chamber demonstrated no significant toxicity of the particles on the surrounding tissues, the study has a limitation that only rabbit corneal endothelial cells, known to have stronger in vivo proliferative capacity than that of HCECs, were investigated [23]. In addition, they only examined a single condition of iron particle concentration that was very similar to the mean iron concentration in the rabbit anterior chamber. Other studies that assessed safety of SPIONs in vitro or in vivo models also have analogous drawbacks [57,58,60]. There is also a report that substantiated magnetic particles with average sizes of a micron scale have exhibited significant toxicities on the rabbit corneal endothelium [61]. Taken altogether, safety of magnetic particles on the corneal endothelium and surrounding tissues has not been fully elucidated yet. Thus, clinical applications of the magnetic force-driven cell delivery approach have still a long way to go despite its remarkable advantages.

CONCLUSION AND FUTURE PERSPECTIVES

Cell-based therapeutic modalities have increasingly attracted much attention as an alternative treatment method of corneal endothelial dysfunction. For the past decades, therapeutic potential of HCECs and HCEPCs has gradually been demonstrated along with development of related cell culture and characterization techniques. However, in comparison to the significant progresses in establishing such techniques, little has been advanced in cell delivery methods. Although simple cell injection methods and tissue engineering-based approaches have shown their promise with therapeutic effects in certain in vitro and in vivo models, they have also presented considerable disadvantages. As an effort to improve the cell injection method, strategies of magnetic force-assisted cell delivery have been employed displaying better cell delivery efficiencies and enhanced therapeutic outcomes. But still, further studies are needed to overcome safety concerns of magnetic particles and translate the cell delivery method to clinical practice.

In the near future, development of multifunctional carriers

for transplantation of engineered corneal endothelium or HCECs would be a key issue to address the problems related to the current cell delivery methods. Existing carriers have not fully provided the necessary properties for maintaining cellular activities of HCECs and facilitating the transplanting procedure. Although advanced carriers have recently been designed using composite materials, their performance has only been partially demonstrated. Further full scale studies are therefore required along with more systematic design of composite material-based carriers. As for the magnetic force-guided cell delivery method, novel cell delivery systems that can evade the direct incorporation of SPIONs in HCECs or HCEPCs would possibly be developed to minimize the toxic effect of the magnetic particles on the cells. For clinical translation of the cell-based therapies for corneal endothelial dysfunction, besides the methodologies of cell delivery, identification of specific markers for HCECs or HCEPCs would be critical to define the differentiation state of the therapeutic cells accurately. So far, the cells have been characterized only by cell phenotype-related properties such as morphologies, functions, and expression of some functional proteins that also exist in other types of cells. In addition, securing autologous cell sources for obtaining the therapeutic cells would be of great importance. Using HCECs or HCEPCs isolated and cultured from the cornea of donors have caused considerable problems such as lack of donors and immune rejection responses. Utilization of autologous stem cells or induced pluripotent stem cells would be a promising alternative to using the allogeneic cells. When these problems are solved along with development of advanced cell delivery methods, the cell-based therapies for corneal dysfunction will truly provide hopes to patients with corneal blindness worldwide.

REFERENCES

1. Bartakova A, Kunzevitzky NJ, Goldberg JL. Regenerative Cell Therapy for Corneal Endothelium. Curr Ophthalmol Rep. 2014; 2: 81-90.
2. Foets BJ, Van den Oord JJ, Volpes R, Missotten L. In situ immunohistochemical analysis of cell adhesion molecules on human corneal endothelial cells. Br J Ophthalmol. 1992; 76: 205-209.
3. Bourne WM. Clinical estimation of corneal endothelial pump function. Trans Am Ophthalmol Soc. 1998; 96: 229-239.
4. Srinivas SP. Cell signaling in regulation of the barrier integrity of the corneal endothelium. Exp Eye Res. 2012; 95: 8-15.
5. Hoffer KJ, Kraff MC. Normal endothelial cell count range. Ophthalmology. 1980; 87: 861-866.
6. Gipson IK. Age-related changes and diseases of the ocular surface and cornea. Invest Ophthalmol Vis Sci. 2013; 54: 48-53.
7. Joyce NC, Navon SE, Roy S, Zieske JD. Expression of cell cycle-associated proteins in human and rabbit corneal endothelium in situ. Invest Ophthalmol Vis Sci. 1996; 37: 1566-1575.
8. Joyce NC. Proliferative capacity of the corneal endothelium. Prog Retin Eye Res. 2003; 22: 359-389.
9. Bourne WM. Biology of the corneal endothelium in health and disease. Eye (Lond). 2003; 17: 912-918.
10. Jhanji V, Mehta JS, Sharma N, Sharma B, Vajpayee RB. Targeted corneal transplantation. Curr Opin Ophthalmol. 2012; 23: 324-329.
11. Parmar T, Ashar JN, Natarajan S. Graft rejection following Descemet stripping automated endothelial keratoplasty: features, risk factors, and outcomes. Am J Ophthalmol. 2012; 153: 949–957.
12. Anshu A, Price MO, Price FW Jr. Risk of corneal transplant rejection significantly reduced with Descemet's membrane endothelial keratoplasty. Ophthalmology. 2012; 119: 536-540.
13. Peh GS, Toh KP, Wu FY, Tan DT, Mehta JS. Cultivation of human corneal endothelial cells isolated from paired donor corneas. PLoS One. 2011; 6: 28310.
14. Peh GS, Toh KP, Ang HP, Seah XY, George BL, Mehta JS. Optimization of human corneal endothelial cell culture: density dependency of successful cultures in vitro. BMC Res Notes. 2013; 6: 176.
15. Yokoo S, Yamagami S, Yanagi Y, Uchida S, Mimura T, Usui T, et al. Human corneal endothelial cell precursors isolated by sphere-forming assay. Invest Ophthalmol Vis Sci. 2005; 46: 1626–1631.
16. Mimura T, Yamagami S, Yokoo S, Araie M, Amano S. Comparison of rabbit corneal endothelial cell precursors in the central and peripheral cornea. Invest Ophthalmol Vis Sci. 2005; 46: 3645-3648.
17. He Z, Campolmi N, Gain P, Ha Thi BM, Dumollard JM, Duband S, Peoc'h M. Revisited microanatomy of the corneal endothelial periphery: new evidence for continuous centripetal migration of endothelial cells in humans. Stem Cells. 2012; 30: 2523-2534.
18. Whikehart DR, Parikh CH, Vaughn AV, Mishler K, Edelhauser HF. Evidence suggesting the existence of stem cells for the human corneal endothelium. Mol Vis. 2005; 11: 816-824.
19. McGowan SL, Edelhauser HF, Pfister RR, Whikehart DR. Stem cell markers in the human posterior limbus and corneal endothelium of unwounded and wounded corneas. Mol Vis. 2007; 13: 1984-2000.
20. Amann J, Holley GP, Lee SB, Edelhauser HF. Increased endothelial cell density in the paracentral and peripheral regions of the human cornea. Am J Ophthalmol. 2003; 135: 584-590.
21. Yamagami S, Yokoo S, Mimura T, Takato T, Araie M, Amano S. Distribution of precursors in human corneal stromal cells and endothelial cells. Ophthalmology. 2007; 114: 433-439.
22. Mimura T, Yamagami S, Usui T, Seiichi, Honda N, Amano S. Necessary prone position time for human corneal endothelial precursor transplantation in a rabbit endothelial deficiency model. Curr Eye Res. 2007; 32: 617–623.
23. Mimura T, Yamagami S, Usui T, Ishii Y, Ono K, Yokoo S, et al . Long-term outcome of iron-endocytosing cultured corneal endothelial cell transplantation with magnetic attraction. Exp Eye Res. 2005; 80: 149-157.
24. Hsu WM, Chen KH, Lai JY, Hsiue GH. Transplantation of human corneal endothelial cells using functional biomaterials: poly(N-isopropylacrylamide) and gelatin. J Exp Clin Med. 2013; 5: 56–64.
25. Shimmura S, Miyashita H, Konomi K, Shinozaki N, Taguchi T, Kobayashi H, et al. Transplantation of corneal endothelium with Descemet's membrane using a hyroxyethyl methacrylate polymer as a carrier. Br J Ophthalmol. 2005; 89: 134-137.
26. Yoeruek E, Saygili O, Spitzer MS, Tatar O, Bartz-Schmidt KU, Szurman P. Human anterior lens capsule as carrier matrix for cultivated human corneal endothelial cells. Cornea. 2009; 28: 416-420.
27. Ishino Y, Sano Y, Nakamura T, Connon CJ, Rigby H, Fullwood NJ, et al. Amniotic membrane as a carrier for cultivated human corneal endothelial cell transplantation. Invest Ophthalmol Vis Sci. 2004; 45: 800-806.
28. Watanabe R, Hayashi R, Kimura Y, Tanaka Y, Kageyama T, Hara S, et al. A novel gelatin hydrogel carrier sheet for corneal endothelial transplantation. Tissue Eng Part A. 2011; 17: 2213-2219.
29. Navaratnam J, Utheim TP, Rajasekhar VK, Shahdadfar A. Substrates for Expansion of Corneal Endothelial Cells towards Bioengineering

of Human Corneal Endothelium. J Funct Biomater. 2015; 6: 917-945.

30. Teichmann J, Valtink M, Nitschke M, Gramm S, Funk R, Engelmann K, et al. Tissue engineering of the corneal endothelium: a review of carrier materials. J Funct Biomater. 2013; 4: 178–208.

31. Wencan W, Mao Y, Wentao Y, Fan L, Jia Q, Qinmei W, et al. Using basement membrane of human amniotic membrane as a cell carrier for cultivated cat corneal endothelial cell transplantation. Curr Eye Res. 2007; 32: 199-215.

32. Amano S, Mimura T, Yamagami S, Osakabe Y, Miyata K. Properties of corneas reconstructed with cultured human corneal endothelial cells and human corneal stroma. Jpn J Ophthalmol. 2005; 49: 448-452.

33. Choi JS, Williams JK, Greven M, Walter KA, Laber PW, Khang G, et al. Bioengineering endothelialized neo-corneas using donor-derived corneal endothelial cells and decellularized corneal stroma. Biomaterials. 2010; 31: 6738-6745.

34. Bayyoud T, Thaler S, Hofmann J, Maurus C, Spitzer MS, Bartz-Schmidt K-U, et al. Decellularized bovine corneal posterior lamellae as carrier matrix for cultivated human corneal endothelial cells. Curr Eye Res. 2012; 37: 179–186.

35. Yoeruek E, Bayyoud T, Maurus C, Hofmann J, Spitzer MS, Bartz-Schmidt KU, et al. Decellularization of porcine corneas and repopulation with human corneal cells for tissue-engineered xenografts. Acta Ophthalmol. 2012; 90: 125–131.

36. Mimura T, Yamagami S, Yokoo S, Usui T, Tanaka K, Hattori S, et al. Cultured human corneal endothelial cell transplantation with a collagen sheet in a rabbit model. Invest Ophthalmol Vis Sci. 2004; 45: 2992-2997.

37. Hsiue GH, Lai JY, Chen KH, Hsu WM. A novel strategy for corneal endothelial reconstruction with a bioengineered cell sheet. Transplantation. 2006; 81: 473-476.

38. Choi JS, Kim EY, Kim MJ, Giegengack M, Khan FA, Khang G, et al. In vitro evaluation of the interactions between human corneal endothelial cells and extracellular matrix proteins. Biomed Mater. 2013; 8: 14108.

39. Yamaguchi M, Ebihara N, Shima N, Kimoto M, Funaki T, Yokoo S, et al. Adhesion, migration, and proliferation of cultured human corneal endothelial cells by laminin-5. Invest Ophthalmol Vis Sci. 2011; 52: 679-684.

40. Kubo M, Sonoda Y, Muramatsu R, Usui M. Immunogenicity of human amniotic membrane in experimental xenotransplantation. Invest Ophthalmol Vis Sci. 2001; 42: 1539-1546.

41. Chen HJ, Pires RT, Tseng SC. Amniotic membrane transplantation for severe neurotrophic corneal ulcers. Br J Ophthalmol. 2000; 84: 826–833.

42. Proulx S, Bensaoula T, Nada O, Audet C, Uwamaliya JD arc, Devaux A, et al. Transplantation of a tissue-engineered corneal endothelium reconstructed on a devitalized carrier in the feline model. Investig Ophthalmol Vis Sci. 2009; 50: 2686–2694.

43. Chen KH, Azar D, Joyce NC . Transplantation of adult human corneal endothelium ex vivo: a morphologic study. Cornea. 2001; 20: 731-737.

44. Amano S. Transplantation of cultured human corneal endothelial cells. Cornea. 2003; 22: S66-74.

45. Proulx S, Audet C, Uwamaliya Jd, Deschambeault A, Carrier P, Giasson CJ, et al. Tissue engineering of feline corneal endothelium using a devitalized human cornea as carrier. Tissue Eng Part A. 2009; 15: 1709-1718.

46. Koizumi N, Sakamoto Y, Okumura N, Okahara N, Tsuchiya H, Torii R et al . Cultivated corneal endothelial cell sheet transplantation in a primate model. Invest Ophthalmol Vis Sci. 2007; 48: 4519-4526.

47. Madden PW, Lai JN, George KA, Giovenco T, Harkin DG, Chirila TV. Human corneal endothelial cell growth on a silk fibroin membrane. Biomaterials. 2011; 32: 4076-4084.

48. Wang T-J, Wang I-J, Lu J-N, Young T-H. Novel chitosan-polycaprolactone blends as potential scaffold and carrier for corneal endothelial transplantation. Mol Vis. 2012; 18: 255–264.

49. Gao X, Liu W, Han B, Wei X, Yang C. Preparation and properties of a chitosan-based carrier of corneal endothelial cells. J Mater Sci Mater Med. 2008; 19: 3611-3619.

50. Proulx S, Brunette I. Methods being developed for preparation, delivery and transplantation of a tissue-engineered corneal endothelium. Exp Eye Res. 2012; 95: 68-75.

51. Anshu A, Price MO, Tan DT, Price FW Jr. Endothelial keratoplasty: a revolution in evolution. Surv Ophthalmol. 2012; 57: 236-252.

52. Price MO, Price FW Jr. Endothelial keratoplasty - a review. Clin Experiment Ophthalmol. 2010; 38: 128-140.

53. Yoon H, Kim EY, Kim H, Park CH, Joo CK, Khang G. Fabrication of transparent silk fibroin film for the regeneration of corneal endothelial cells; preliminary study. Macromol Res. 2014; 22: 297–303.

54. Mimura T, Shimomura N, Usui T, Noda Y, Kaji Y, Yamgami S, et al. Magnetic attraction of iron-endocytosed corneal endothelial cells to Descemet's membrane. Exp Eye Res. 2003; 76: 745-751.

55. Wang YX, Hussain SM, Krestin GP. Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging. Eur Radiol. 2001; 11: 2319-2331.

56. Clément O, Siauve N, Cuénod CA, Frija G. Liver imaging with ferumoxides (Feridex): fundamentals, controversies, and practical aspects. Top Magn Reson Imaging. 1998; 9: 167-182.

57. Patel SV, Bachman LA, Hann CR, Bahler CK, Fautsch MP. Human corneal endothelial cell transplantation in a human ex vivo model. Invest Ophthalmol Vis Sci. 2009; 50: 2123-2131.

58. Moysidis S, Alvarez-Delfin K, Peschansky VJ, Salero E, Weisman AD, Bartakova A, et al. Magnetic field-guided cell delivery with nanoparticle-loaded human corneal endothelial cells. Nanomedicine. 2015; 11: 499-509.

59. Sakhtianchi R, Minchin RF, Lee KB, Alkilany AM, Serpooshan V, Mahmoudi M. Exocytosis of nanoparticles from cells: role in cellular retention and toxicity. Adv Colloid Interface Sci. 2013; 201-202: 18-29.

60. Bi YL, Wu MF, Lu LX, Zhou Q, Du F, Sun XT, et al. Functions of corneal endothelial cells do not change after uptake of superparamagnetic iron oxide nanoparticles. Mol Med Rep. 2013; 7: 1767-1772.

61. Raju HB1, Hu Y, Vedula A, Dubovy SR, Goldberg JL. Evaluation of magnetic micro- and nanoparticle toxicity to ocular tissues. PLoS One. 2011; 6: 17452.

Cite this article

Kim H, Shin YJ, Lee J (2016) Recent Strategies of Therapeutic Cell Delivery for Regeneration of Corneal Endothelium. JSM Biotechnol Bioeng 3(1): 1047.