Progress in Retinal and Eye Research 35 (2013) 1–17

Contents lists available at SciVerse ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Corneal endothelial regeneration and tissue engineering

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ARTICLE INFO

Article history:
Available online 23 January 2013

Keywords:
Review
Corneal endothelium
Descemet stripping automated endothelial keratoplasty
Tissue engineering
Transplantation
Wound healing

ABSTRACT

Human corneal endothelial cells (HCECs) have a limited proliferative capacity. Descemet stripping with automated endothelial keratoplasty (DSAEK) has become the preferred method for the treatment of corneal endothelial deficiency, but it requires a donor cornea. To overcome the shortage of donor corneas, transplantation of cultured HCEC sheets has been attempted in experimental studies. This review summarizes current knowledge about the mechanisms of corneal endothelial wound healing and about tissue engineering for the corneal endothelium. We also discuss recent work on tissue engineering for DSAEK grafts using cultured HCECs and HCEC precursor cell isolation method (the sphere-forming assay). DSAEK grafts (HCEC sheets) were constructed by seeding cultured HCECs on human amniotic membrane, thin human corneal stroma, and collagen sheets. The pump function of the HCEC sheets thus obtained was approximately 75%–95% of that for human donor corneas. HCEC sheets were transplanted onto rabbit corneas after DSAEK. While the untransplanted control group displayed severe stromal edema, the transplanted group had clear corneas throughout the observation period. The sphere-forming assay using donor human corneal endothelium or cultured HCECs can achieved mass production of human corneal endothelial precursors. These findings indicate that cultured HCECs transplanted after DSAEK can perform effective corneal dehydration in vivo and suggest the feasibility of employing the transplantation of cultured HCECs to treat endothelial dysfunction. Additionally, corneal endothelial precursors may be an effective strategy for corneal endothelial regeneration.

Contents

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[1] Percentage of work contributed by each author in the production of the manuscript is as follows: Tatsuya Mimura: 50%; Satoru Yamagami: 25%; Shiro Amano: 25%.

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http://dx.doi.org/10.1016/j.preteyeres.2013.01.003

1. Introduction

1.1. Structure and function of corneal endothelium

Corneal endothelial cells (CECs) are believed to arise from the neural crest (Johnston et al., 1979; Bahn et al., 1984) and form a monolayer of hexagonal cells that acts as a barrier between the corneal stroma and the aqueous humor in the anterior chamber. Transparency of the cornea is maintained by regulating stromal hydration through the barrier and pump functions of the corneal endothelium. Human CECs (HCECs) normally display limited proliferative capacity in vivo (Wilson et al., 1993, 1995; Egan et al., 1998; Senoo and Joyce, 2000; Senoo et al., 2000), because they are arrested in Gl phase (Joyce et al., 1996a,b). Therefore, the number of HCECs gradually decreases with age (Murphy et al., 1984; Bourne et al., 1997; Hollingsworth et al., 2001) and declines dramatically after endothelial damage due to trauma, phacoemulsification, or acute angle-closure glaucoma. Corneal endothelial damage has been directly implicated in causing bullous keratopathy because of the relative lack of endothelial cell proliferative capacity. Penetrating keratoplasty (PKP) has long been performed as the initial treatment for CEC dysfunction. In fact, more than half of the patients who undergo full-thickness corneal transplantation have impaired visual acuity that is entirely due to corneal endothelial problems and their corneal epithelium is normal (Mannis and Krachmer, 1981; Rapuano et al., 1990; Cosar et al., 2002). Corneal transplantation requires a fresh human cornea, but there is a worldwide shortage of donors.

1.2. History of corneal endothelial tissue engineering

To overcome this donor cornea shortage, transplantation of cultured HCEC sheets has been tested in experimental studies as a substitute for full-thickness corneal transplantation. Cultured HCECs derived from adult human donor corneas have been transplanted onto denuded Descemet's membrane (Insler and Lopez, 1986, 1991a,b; Engelmann and Friedl, 1989; Engelmann et al., 1999; Aboalchamat et al., 1999; Bohnke et al., 1999; Chen et al., 2001; Amano, 2002, 2003; Mimura et al., 2004a), collagen matrix (Mimura et al., 2004b), amniotic membrane (Ishino et al., 2004), human corneal stromal discs (Honda et al., 2009; Choi et al., 2010), gelatin hydrogel discs (Lai et al., 2007; Watanabe et al., 2011), and chitosan-based membrane (Liang et al., 2011) ex vivo. Although culture of HCECs from donor corneas yields cells with HCEC-like morphology and function, the cultured cells become increasingly heterogeneous with an increase of donor age or a greater number of passages (Miyata et al., 2001; Zhu and Joyce, 2004; Joyce and Zhu, 2004). In addition, the density of HCECs, which is a pivotal factor in maintaining long-term corneal transparency, decreases after transplantation of HCEC sheets as well as after conventional PKP (Mimura et al., 2004b). Thus, a high cell density and normal hexagonal cells with adequate endothelial function are crucial requirements for obtaining cultured HCEC sheets that are comparable with or better than donor corneas.

1.3. Use of cultured HCECs for Descemet stripping with automated endothelial keratoplasty

Over the last few years, Descemet stripping with automated endothelial keratoplasty (DSAEK) has become a standard procedure for corneal transplantation in patients with endothelial dysfunction (Gorovoy, 2006; Koenig and Covert, 2007; Price et al., 2008; Terry et al., 2008). DSAEK achieves better postoperative visual function and reduces the risks associated with penetrating keratoplasty, such as severe astigmatism and expulsive hemorrhage. Furthermore, Descemet membrane endothelial keratoplasty (DMEK) and Descemet membrane automated endothelial keratoplasty (DMAEK) are the next steps for endothelial keratoplasty (Terry, 2012). This procedure can provide faster visual rehabilitation, minimize postoperative ocular surface complications, and preserve endothelial cell density compared DSAEK (Dapena et al., 2011; Guerra et al., 2011; Laaser et al., 2012; Parker et al., 2012; Naveiras et al., 2012; Krabcova et al., 2012; Terry, 2012). However, DSAEK, DMEK, or DMAEK require a donor cornea, so the worldwide shortage of donor corneas limits its application. If cultured HCECs could be used for corneal transplantation, many patients with corneal endothelial dysfunction could be treated by using cells from a single donor cornea. Therefore, he feasibility of DSAEK using cultured HCECs has been investigated (Mimura et al., 2004b; Honda et al., 2009). In this review, we discuss the mechanisms of corneal endothelial wound healing and provide an overview of tissue engineering for the corneal endothelium with cultured CECs, focusing on recent studies into the feasibility of transplanting cultured HCEC sheets and human corneal endothelial precursors. All studies described here were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Human donor corneas were handled according to the tenets of the Declaration of Helsinki of 1975 and its 1983 revision.

2. Healing of corneal endothelium

2.1. Growth capacity of HCECs

Healing of corneal endothelial wounds occurs predominantly by migration and enlargement of existing cells rather than by