Available online at www.sciencedirect.com

ScienceDirect

Reactive & Functional Polymers 67 (2007) 1284–1291

REACTIVE & FUNCTIONAL POLYMERS

www.elsevier.com/locate/react

Functional biomedical polymers for corneal regenerative medicine

Jui-Yang Lai [a,b], Ging-Ho Hsiue [c,*]

[a] Institute of Biochemical and Biomedical Engineering, Chang Gung University, Taoyuan 33302, Taiwan, ROC
[b] Molecular Medicine Research Center, Chang Gung University, Taoyuan 33302, Taiwan, ROC
[c] Department of Chemical Engineering, National Tsing Hua University, Hsinchu 30013, Taiwan, ROC

Received 30 June 2007; received in revised form 26 July 2007; accepted 26 July 2007
Available online 19 August 2007

Dedicated to Professor Teiji Tsuruta on the occasion of his 88th birthday (Beiju).

Abstract

Recent progress in biomedical polymer science has greatly contributed to rapid development of corneal regenerative medicine. In the past decades, scientists have achieved several major breakthroughs in corneal tissue reconstruction. Studies regarding the findings of core-and-skirt keratoprostheses for visual rehabilitation, biosynthetic tissue replacements for corneal transplantation, and thermo-responsive cell-detachable substrates for corneal cell sheet engineering have been reported by several groups of investigators. This brief overview focuses on the contributions of functional polymers in the applications of corneal regenerative medicine. The keratoprosthetic devices developed by our group using heterobifunctional silicone rubber membranes grafted with different bioactive functional groups showed promising results in animal studies. In addition, the fabrication and transplantation of bioengineered human corneal endothelial cell sheets by utilizing the functional biomedical polymers such as poly(*N*-isopropylacrylamide) and gelatin are discussed, especially for the significance of gelatin in the development of a potential intraocular delivery system for cell sheet grafts.

Keywords: Functional biomedical polymers; Polymer modification; Corneal regenerative medicine; Keratoprosthesis; Cell sheet engineering

1. Introduction

In the human body, the eye is one of the most complex and remarkable organs. The cornea is the transparent circular part of the front of the eyeball that covers the pupil, iris, and anterior chamber. It is composed of five distinct anatomic layers including epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. Corneal transplantation may restore vision when the cornea has become opacified as a result of hereditary diseases, infection, or injury. However, the shortage of donor corneal tissue has driven the expansion of research on keratoprosthesis for treatment of

* Corresponding author. Tel.: +886 3 571 9956; fax: +886 3 572 6825.
E-mail address: ghhsiue@che.nthu.edu.tw (G.-H. Hsiue).

1381-5148/$ - see front matter
doi:10.1016/j.reactfunctpolym.2007.07.060

corneal blindness. Functional biomedical polymers have attracted much attention for their potential applications in the field of keratoprosthetic devices. In recent years, the development of biomimetic materials as tissue-engineered corneal replacements also showed very encouraging results. On the other hand, scientists have now achieved a major breakthrough in corneal epithelial regeneration. The revolutionary design of thermo-responsive cell harvest system enables novel cell sheet techniques for engineering tissue replacements without scaffolds. Carrier-free and sutureless transplantation of autologous oral mucosa epithelial cell sheets may represent an effective way to treat patients with several bilateral limbal stem cell deficiency. Although the improvements in ocular surface reconstruction are impressive, the occurrence of corneal opacities is closely related to endothelial dysfunction in most patients requiring corneal transplantation. It is expected that the cell sheet-based therapy will give promising hope of a possible treatment of corneal endothelium deficiency. This overview will provide an insight into the various functional biomedical polymers that are useful in corneal regenerative medicine.

2. Keratoprosthesis

When a progressive corneal ulceration or a penetrating corneal injury with tissue loss occurs, emergency penetrating keratoplasty or lamellar keratoplasty is carried out to restore ocular integrity and to avoid further complications, such as extensive chamber angle synechia, angle closure glaucoma, and endophthalmitis. Although corneal transplantation has a high success rate, the shortage of donor corneas remains a worldwide problem. The development of artificial corneas (keratoprostheses) is a promising alternative to obtain biosynthetic tissue replacements for corneal transplantation. In 1771, French ophthalmologist Guillaume Pellier de Quengsy [1] first suggested inserting a glass plate into opaque corneas to restore clear vision. The first experimental implantation was performed by von Nussbaum and Nepomuk [2] in 1856, using rabbits as an experimental model. In 1859, human implantation was first attempted when Heusser [3] placed a glass implant into the cornea of a 19-year-old patient. Polymer has become the most popular substance of choice for keratoprosthesis research following World War II. The keratoprosthesis developed by Stone and Herbert [4] consisted of a central optical core with a marginal part for anchoring of a perforated plastic. They found that the fragments made of poly(methyl methacrylate) (PMMA) were well tolerated in the cornea. In the 1960s, investigators focused on the design of core-and-skirt keratoprosthetic models. A plastic fiber meshwork supporting plate, i.e., Cardona implant, was first studied for keratoprosthesis [5,6]. The second generation of keratoprosthesis, Girard keratoprosthesis, was reported based on the modification of the original Cardona implant [7]. In addition to PMMA, other materials such as silicone [8] and ceramic [9] have also been used for preparation of keratoprosthetic devices. Although the design of keratoprosthesis has significantly improved, the persistence of a high incidence of failure suggests that successful development of keratoprosthetic implants remains an extremely difficult task [10]. Previous attempts failed due to erosion and necrosis of the adjacent tissue, chronic inflammation, and epithelialization of the anterior chamber [11–13]. Optimally, the anterior surface of a keratoprosthesis should support the adherence and proliferation of corneal epithelial cells, subsequently resulting in an intact epithelial layer which is continuous with the surrounding host epithelium. A continuous layer of epithelial cells permits maintenance of the normal precorneal tear film, ensures a good optical surface, and provides a barrier against microbial invasion.

In 1991, Kirkham et al. [14] found that the PMMA intracorneal keratoprosthesis coated with type I collagen could be used to improve the biocompatibility of an implant. In another study, Ikada et al. [15] reported that poly(vinyl chloride) (PVC) hydrogel immobilized with collagen in contact lens could feasibly be used as keratoprosthetic devices. A variety of synthetic polymers such as poly(vinyl alcohol-*co*-vinyl acetate) copolymer [16], polybutylene/polypropylene blend [17,18], poly(tetrafluoroethylene) (PTFE) [19,20], polyurethane [21], polysiloxane [22], and poly(2-hydroxyethyl methacrylate) (PHEMA) [23–25] have recently been investigated for their potential use in keratoprosthesis. The preparation of artificial cornea has already been studied in our laboratory for quite some time [26–31]. It is found that four important issues must be addressed if an ideal keratoprosthesis is to be obtained. First, the anterior surface of implant is required to be completely covered with epithelium by promotion of cell growth. Secondly, epithelial downgrowth has to be suppressed when