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A collagen-based corneal stroma substitute with micro-designed architecture

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A 3D corneal stroma substitute with micro-level patterns was constructed from a stack of 4 micro patterned collagen or collagen–elastin like recombinamer (Col:ELR) blend layers. The transparency of all of the films was quite high with the uncrosslinked (UXL) films and dehydrothermally treated (150 °C, 24 h) Col:ELR films yielding the best results. Human corneal keratocytes (HK) could be attached and proliferated equally well on the single films of Col and Col:ELR. However, for the multilayer constructs the proliferation was higher on Col than on Col:ELR. The cells were found to align along the patterns (microchannels with a 39 μm groove depth, 8 μm groove width, 3.3 μm ridge width, and 54.7° inclination angle) of the films, while no significant alignment was observed on the unpatterned films. The transparency of the seeded Col:ELR films was superior to the Col films over a 30 day incubation period and was quite close to that of a native human cornea. It was concluded that the Col and Col:ELR films and their 3D constructs have significant potential for use as corneal stroma substitutes.

Introduction

The cornea is the transparent exterior part of the eye and is about 500 μm thick. It protects the eye from external objects and functions as the principle optical element, refracting 70% of any incoming light.[1] The stroma is the thickest part of the cornea, which consists of 200–400 lamellae that are parallel to the cornea surface, but orthogonal to adjacent lamellae, forming a plywood-like structure that is populated by keratocytes. The organization of the lamellae and fibrils is essential for the biomechanical and optical properties of the cornea[2,3] and is made up of collagen types I and V, and proteoglycans. Any disruption of the organization of collagen or proteoglycans, like keratocan and lumican, leads to a decrease in the transparency of the cornea.[4–6]

Corneal diseases and wounds are the next major causes of blindness after cataracts. There are about 27.9 million blind people worldwide and of these 4.9 million have bilateral corneal blindness.[7] Today, cornea transplantation is the only effective treatment for corneal blindness and it is more successful than other solid organ transplantations due to the avascular nature of the cornea.[8] However, a shortage of donor corneas and the risks of disease transmission and immune rejection make the replacement of a damaged cornea with an artificial substitute a promising alternative. At present, keratoprostheses (KPro) that use synthetic polymers like PHEMA[9] and PMMA[10] are the only options for patients with a history of several corneal graft rejections and problems including calcification, infection and retinal detachment. Osteo-odonto KPro (OOKP), Boston KPro, and AlphaCor KPro are the three most commonly used keratoprostheses. A common property of these keratoprostheses is their core-and-skirt design, which aims to achieve good integration between the prosthesis and the host tissue and a higher clinical success rate.[9,11] However, the development of glaucoma, retinal detachment and necrosis are still remaining problems that can be associated with keratoprostheses.[12] Tissue engineered products that can simulate the organization of a natural cornea are expected to help eliminate the problems associated with transplantation and keratoprostheses. Several tissue engineering approaches have been used to reconstruct the cornea involving natural and/or synthetic materials. Most of these studies have focused on the construction of split thickness corneas, composed of one layer that substitutes for either the epithelial,[13,14] stromal[15,16] or endothelial layers[17,18], or two layer hemi-corneas, composed of epithelial and stromal layers.[19,20] Several other attempts have been made to construct a full thickness cornea using tissue engineering.[21,22] Foams, hydrogels and meshes may provide optimal conditions for cell growth and can be transparent enough, however, none of these scaffolds are able to properly

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