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Review

Ocular surface reconstruction using stem cell and tissue engineering

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ABSTRACT

Most human sensory information is gained through eyesight, and integrity of the ocular surface, including cornea and conjunctiva, is known to be indispensable for good vision. It is believed that severe damage to corneal epithelial stem cells results in devastating ocular surface disease, and many researchers and scientists have tried to reconstruct the ocular surface using medical and surgical approaches. Ocular surface reconstruction via regenerative therapy is a newly developed medical field that promises to be the next generation of therapeutic modalities, based on the use of tissue-specific stem cells to generate biological substitutes and improve tissue functions. The accomplishment of these objectives depends on three key factors: stem cells, which have highly proliferative capacities and longevities; the substrates determining the environmental niche; and growth factors that support them appropriately. This manuscript describes the diligent development of ocular surface reconstruction using tissue engineering techniques, both past and present, and discusses and validates their future use for regenerative therapy in this field.

Contents

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1. Introduction

The concept of an “ocular surface” is widely recognized in the field of ophthalmology, and our understanding of the role of ocular surface biology and immunology has been greatly improved by the numerous research studies carried out in this field (Thoft and Friend, 1979). Although the normal ocular surface comprises only 1/6 of the outer wall of the eye, it supports several of the eye's major functions, as it is covered with highly specialized corneal and conjunctival epithelia, formed by two phenotypically different types of epithelial cell. Over the past thirty years, several scientific discoveries such as the identification of corneal epithelial stem cells, the establishment of novel methods in epithelial culturing and the understanding of extracellular matrices and growth factors have enabled a novel surgical approach to treatment of ocular surface disorders, using regenerative medicine.

Based on tissue engineering, regenerative medicine is a newly developed area that uses somatic stem cells to generate biological substitutes and improve tissue functions (Langer and Vacanti, 1993). Success depends on three key factors: stem cells, extracellular matrices and growth factors. A variety of trials are currently in development, based on the utilization of stem cells and appropriate substrates to produce substitutes capable of reconstructing damaged and diseased tissues. In the field of ophthalmology, the production of tissue organs *in vitro* shows great promise, especially with regard to the anterior segment of the eye (Pellegrini et al., 1997).

Severe ocular surface disease (OSD) due to thermal and chemical burns, Stevens-Johnson syndrome (SJS), ocular cicatricial pemphigoid (OCP) or other conditions currently poses a serious clinical challenge for ophthalmologists worldwide. In these cases, the corneal epithelial stem cells located in the corneal limbus are destroyed, and coverage of the corneal surface by invading neighboring conjunctival epithelial cells results in neovascularization, chronic inflammation, ingrowth of fibrous tissue and stromal scarring. This severely compromises the ocular surface and seriously diminishes visual acuity (Chiou et al., 1998; Kinoshita et al., 2001; Tseng, 1989). Conventional treatment methods have generally proved unsatisfactory, and the long-term consequences of these ocular disorders are devastating. Clinically useful and effective surgical techniques for ocular surface reconstruction (OSR) are therefore needed for such patients.

In this present paper, we describe the history, recent advances, current developments and future challenges relating to OSR in both its basic science and clinical aspects, as well as providing novel clinical information for the treatment of severe OSD.

2. Ocular surface reconstruction

The concept of OSR is widely accepted in the field of ophthalmology, and our understanding of the role of the ocular surface has been greatly improved by numerous research studies. Various surgical procedures have been developed over the past 30 years to treat and reconstruct severely damaged or diseased ocular surface epithelia.

2.1. Conjunctival transplantation, keratoepithelioplasty and limbal transplantation

The concept of OSR was first reported in relation to an autologous conjunctival transplantation for unilateral chemical injury in Thoft's description of conjunctival tissue transplantation for unilaterally affected chemical injuries (Thoft, 1977). The surgery was performed by removing pathological scarred tissue from a patient's corneal surface and placing four pieces of conjunctival autograft taken from the contralateral eye at the limbus in order to reconstruct the cornea by regenerating conjunctival epithelial cells from these autografts. Subsequently, Thoft described the similar surgical technique of keratoepithelioplasty (Thoft, 1984), which employed a different tissue source (donor corneal lenticules) to regenerate corneal epithelial cells. Although the concept of corneal epithelial stem cells was not established at that time, the cell-level biological differences between regenerated corneal and conjunctival epithelia were known. Over time, keratoepithelioplasty has gradually gained acceptance despite initial disputes among researchers because it is a form of epithelial allograft (Kaufman, 1984). In fact, keratoepithelioplasty has proved to be dramatically effective in treating peripheral corneal ulcers, including Mooren's ulcer (Kinoshita et al., 1991), supplying both a regenerated corneal epithelium and an appropriate corneal substrate for inhibiting conjunctival invasion onto the cornea. Sun's group proposed the corneal limbal stem cell concept (Schermer et al., 1986), which had a tremendous impact on the development of keratoepithelioplasty, leading to autologous limbal transplantation (LT) (Kenyon and Tseng, 1989). Tsai and Tseng then introduced allogenic LT, aimed at achieving a permanent lifespan for regenerated corneal epithelium by means of stem cell transplantation, although intensive immunosuppressive therapy was also needed (Tsai and Tseng, 1994). These surgical procedures are classed as “cellular surgery”—a form of primitive regenerative