Advanced Drug Delivery Reviews xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Wound healing in the eye: Therapeutic prospects

Mohammed Ziaei, Carol Greene, Colin R. Green *

University of Auckland, Department of Ophthalmology, New Zealand National Eye Centre, New Zealand

ARTICLE INFO

Article history:
Received 10 July 2017
Received in revised form 6 October 2017
Accepted 10 January 2018
Available online xxxx

Keywords:
Cornea
Epithelium
Stroma
Persistent epithelial defect
Wound healing

ABSTRACT

In order to maintain a smooth optical surface the corneal epithelium has to continuously renew itself so as to maintain its function as a barrier to fluctuating external surroundings and various environmental insults. After trauma, the cornea typically re-epithelializes promptly thereby minimizing the risk of infection, opacification or perforation. A persistent epithelial defect (PED) is usually referred to as a non-healing epithelial lesion after approximately two weeks of treatment with standard therapies to no avail. They occur following exposure to toxic agents, mechanical injury, and ocular surface infections and are associated with significant clinical morbidity in patients, resulting in discomfort or visual loss. In the case of deeper corneal injury and corneal pathology the wound healing cascade can also extend to the corneal stroma, the layer below the epithelium. Although significant progress has been made in recent years, pharmaco-therapeutic agents that promote corneal healing remain limited. This article serves as a review of current standard therapies, recently introduced alternative therapies gaining in popularity, and a look into the newest developments into ocular wound healing.

1. Introduction

This review will consider two aspects of wound healing in the eye: repair and maintenance of the corneal epithelium which faces the external environment, and maintenance of the corneal stroma which provides the cornea's structural integrity.

To maintain a smooth optical surface, the corneal epithelium has to continuously renew itself to function as a barrier to fluctuating external surroundings and various environmental insults. After trauma the cornea typically re-epithelializes promptly, minimizing the risk of infection, opacification or perforation. In the presence of certain risk factors such as dry eye disease, diabetic keratopathy, ocular cicatrizing disorders, limbal stem cell deficiency (LSCD), chemical injury, exposure keratopathy, and neurotrophic keratopathy from prior herpetic keratitis or previous keratoplasty; epithelial defects can persist. A persistent epithelial defect (PED) is usually referred to a non-healing epithelial lesion after approximately two weeks of treatment with standard therapies to no avail [1]. They occur following exposure to toxic agents, mechanical injury or ocular surface infections and are associated with significant clinical morbidity in patients, resulting in discomfort or visual loss. The incidence of PEDs is unknown but estimated to about 200,000 per annum in the USA although significantly higher in some other parts of the world. Management of patients with PEDs can be challenging and may require an extended treatment and follow-up period. Although significant progress has been made in recent years, pharmaco-therapeutic agents that promote epithelial healing remain limited. In this article a review of current standard therapies, recently introduced alternative therapies gaining in popularity, and a look into the newest developments into ocular surface wound healing is given.

1.1. The corneal epithelium

The corneal epithelium is an ectoderm derived, non-keratinized, stratified layer with a unique cytokeratin expression pattern and a reported thickness of between 48 and 53 μm [2,3]. The corneal epithelium is a barrier composed of a series of tightly networked cells seven to eight cell layers thick and attached to the basal lamina through hemidesmosomes. Cells are attached to each other with desmosomes and communicate both within and between layers via gap junctions. The epithelium serves as the eyes first line of defense against trauma. It is a fast regenerating tissue that is maintained by the integrity and functionality of a specialized stem cell population, known as limbal stem cells (LSCs). LCS are said to be located in the basal layer of the palisades of Vogt of the limbus, a narrow transition zone surrounding the cornea [4].

Regeneration of the corneal epithelial surface after an intrinsic or extrinsic insult appear to involve division, migration, and maturation of LSCs. The XYZ hypothesis proposes that the maintenance of the corneal epithelium can be represented by the formula X + Y = Z, where Z

* Corresponding author at: Department of Ophthalmology, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.
E-mail address: c.green@auckland.ac.nz (C.R. Green).

https://doi.org/10.1016/j.addr.2018.01.006
0169-409X/

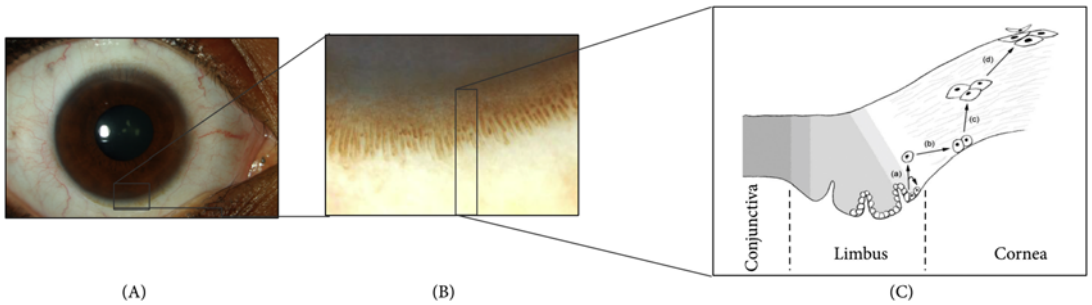

Fig. 1. (A) Overview of the anterior surface of the human eye, in which the sclera (with overlying conjunctiva) and cornea can be easily discriminated. (B) The limbus is highly pigmented in some individuals, and allows clear visualization of the limbal palisades of Vogt. (C) Diagram of a cross section through the conjunctival, limbal and corneal epithelium. Limbal progenitor cells (a) differentiate into transient amplifying cells (b), post-mitotic cells (c) and finally terminally differentiated cells (d). Movement of cells in X, Y, Z direction is presented by proliferation of stem cells (a), differentiation and centripetal migration (b, c), and desquamation (d) respectively. Reproduced from [6] with permission.

(desquamation), is the sum of X (proliferation) and Y (centripetal migration) (Fig. 1) [5,6].

1.2. The wound healing response

The wound healing response in the cornea is a convoluted process. An intrinsic cascade involving autocrine and paracrine cytokine mediated interactions between epithelial cells, stromal keratocytes, corneal nerves, and cells of the immune system control this process. The tissue wound healing response also varies depending on the severity of the inciting injury. Upon injury, epithelial cells evoke sequential steps attempting to efficiently seal the wound and to prevent potential opportunistic infection that can result in devastation of the eye. Epithelial wound healing occurs in a phased process with specific physiological functions [7].

In the latent phase there is no movement of cells or any apparent change in cell numbers but there is reported to be an increase in metabolic activity and a reorganization of cell structures is observed [8,9]. This is accompanied by an increased synthesis of several cytoskeletal proteins with several integrins e.g. α6 and β4, located at the basal area of epithelial cells responsible for the linkage of cytoskeletal components to the underlying basement membrane [10]. In the migration phase, cells around the wound edge migrate across and cover the denuded area [11], a process which requires the synthesis of an array of actin-rich stress fibers in the cytoplasm and which can be readily blocked if topical anesthetic drugs are used [12]. This is followed by the cell proliferation stage in which epithelial cells divide and differentiate in order to restore the epithelium's original structure and complete with intercellular junctions [13]. The proliferative response appears to be compartmentalized to the limbal region with cells at the leading edge not showing an increased rate of proliferation [14]. The last phase is characterized by the establishment of cell to substrate attachments as the epithelium is stabilised and is no longer motile [15]. These phases are often overlapping and allow for the coverage of the wounded epithelium, restoration of normal cell density and reformation of cell attachments. PEDs occur when there is a failure of mechanisms which promote corneal epithelialization.

1.3. Wound healing modulation

The first step in the management of any epithelial abnormality is to determine and address the underlying aetiology. Numerous pharmacological agents are currently employed to modify wound healing in patients with a PED. Patients are currently treated using a step ladder management approach utilizing a series of interventions. We will now review some of the currently available and emerging pharmaceutical agents. It is beyond the scope of this article to discuss surgical treatment options such as tarsorrhaphy, therapeutic excimer laser ablation and amniotic membrane transplantation.

2. Traditional treatment strategies for the ocular surface

2.1. Discontinuation of medication

The first goal when dealing with a PED is to provide the eye with an environment conducive to the innate healing ability of the ocular surface. An often overlooked cause of poor ocular healing is "medicamentosa" or toxic keratitis stemming from topical ophthalmic medication or preservatives in eye drops. Preservatives such as benzalkonium chloride (BAK) and Polyquarternium-1 are typical culprits as they are almost ubiquitously deployed in ophthalmic preparations and have consistently been shown to have toxic effects in laboratory, experimental, and clinical studies [16–19]. In the setting of a PED, switching to preservative free medication or a different agent or stopping treatment altogether may prove to be curative.

2.2. Tear substitutes and lubricants

Pharmaceutical tear substitutes provide lubrication but not nutrition. Aggressive lubrication is typically a first-line therapy in dealing with patients with a PED. This typically involves frequent application of preservative-free drops or sterile ophthalmic ointment [20]. Various pharmacological lubricant preparations are currently available to treat PED include hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol, and povidine and sodium hyaluronate. Whilst topical administration of such lubricants appears to accelerate the healing of the corneal epithelium [21,22], lubricants alone are generally insufficient to treat PED [23].

2.3. Corticosteroids

Glucocorticoids are reported to be synthesized naturally in the human ocular surface and regulate over 4000 genes in human corneal epithelial cells [24]. In the cornea, glucocorticoids inhibit blood and lymphatic vessel growth, reduce inflammation and increase epithelial integrity under hypoxic conditions [24].

Although much research has been done on the effect of steroids on corneal wound healing, the results remain contradictory with the molecular mechanism of action of steroids yet to be fully characterized. Traditionally, steroids have been thought to hinder epithelial wound healing as they inhibit fibroblastic activity (65), reduce epithelial cell migration [24] and increase the risk of secondary microbial keratitis [25,26]. On the other hand, there are a number of animal and human studies that report the use of steroids to be safe with no significant effect on corneal epithelial wound healing times [27–29]. Corticosteroids have also not been shown to affect the minimum inhibitory concentration of antibiotics or the proliferation of organism in vitro [30–33], but the long-term use of topical corticosteroids may increase the risk of corneal perforation and can lead to glucocorticoid induced glaucoma and cataract. They are therefore used sparingly in patients with PED and often

Please cite this article as: M. Ziaei, et al., Wound healing in the eye: Therapeutic prospects, Adv. Drug Deliv. Rev. (2018), https://doi.org/10.1016/j.addr.2018.01.006