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Dacryology Update

Human lacrimal gland regeneration Perspectives and review of literature

Shubha Tiwari, M.Pharm [a]; Mohammad Javed Ali, MS, FRCS [b]; Geeta K. Vemuganti, MS, FNAMS [a,c,*]

Abstract

The human lacrimal gland is an essential component of the lacrimal functional unit (LFU). Any perturbation of this unit can lead to the debilitating morbid condition called the dry eye syndrome (DES). The current line of therapy available for dry eye remains supportive and palliative with the patient being dependent on life long and frequent administration of lubricating eye drops. Even advanced therapies like punctual plugs, cyclosporine B administration, and salivary gland auto-transplantation have led to a limited success. Under these scenarios, the option of cell based therapy needs to be explored to provide better and long term relief to these patients. This review gives an overview of the efforts in lacrimal gland regeneration and examines the past and ongoing research in cell based therapies in animals as well as human lacrimal gland cultures. The authors discuss their first of its kind functionally viable human lacrimal gland *in vitro* culture system from fresh exenteration specimens. A brief overview of research in near future and the potential implications of lacrimal gland regenerative therapies have been discussed.

Keywords: Lacrimal gland, Regeneration, Dry eye, Stem cells

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Introduction

The human lacrimal gland is an essential component of the lacrimal functional unit (LFU) which comprises of the lacrimal gland, the ocular surface (cornea, conjunctiva and the meibomian gland) and the associated sensory and motor nerves (Figure 1). The LFU controls the secretion of the major components of the tear film and is overall responsible for maintaining the stability of the tear film, transparency of the cornea and the quality of the image projected onto the retina.[1]

Any perturbation in the stability of the tear film leads to destabilization of the ocular surface which, over a period of time, can lead to the debilitating morbid condition called the dry eye syndrome (DES). The composition of the tear film can be altered due to the dysfunction of either the lacrimal gland or the meibomian glands; however for the purpose of this review we will restrict our discussion to lacrimal gland dysfunction. Lacrimal gland dysfunction and destruction is seen in cases of advancing age, autoimmune disorders, orbital radiotherapy, low androgen pool etc. This lacrimal dysfunction causes hyperosmolarity of tear film resulting in a vicious loop of ocular surface inflammation which is responsible for ocular epithelial damage leading to corneal ulceration and eventual decline in visual acuity.[1]

The current line of therapy available for dry eye remains supportive and palliative with the patient being dependent on life long, frequent administration of lubricating or hydrating eye drops. Even advanced therapies like punctal plugs, cyclosporine B administration, and salivary gland auto-transplantation have led to a limited success. Under these scenarios, the option of cell based therapy needs

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[a] Sudhakar and Sreekant Ravi Stem Cell Biology Laboratory, L. V. Prasad Eye Institute, Hyderabad, India
[b] Dacryology Service, L. V. Prasad Eye Institute, Hyderabad, India
[c] School of Medical Sciences, University of Hyderabad, Hyderabad, India

* Corresponding author at: School of Medical Sciences, University of Hyderabad, Hyderabad, India. Tel.: +91 4030612345.
e-mail address: gkvemuganti@gmail.com (G.K. Vemuganti).

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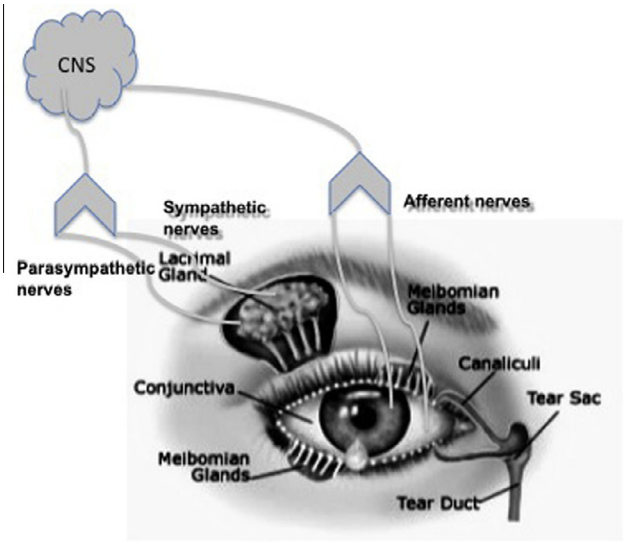

Figure 1. The lacrimal functional unit.

to be explored to provide better and long term relief to these patients.

Histology, anatomy and physiology

The lacrimal gland is a tubulo-acinar exocrine gland that consists of secretory columnar epithelium arranged in a lobular pattern. These secretory acinar cells empty their secretions into ducts that anastomose into larger excretory ducts which drain onto the ocular surface. Both the acinar and the ductal cells have numerous vesicles in their apical portion while the base is associated with a basement matrix. Enveloping the secretory acinar cells are myoepithelial cells that contract and squeeze them enabling the draining of the secretory components into the ducts. Between the lacrimal lobes are fibroblasts, which produce the collagen and matrix of interstitial spaces, and mast cells, which secrete histamine and heparin. In addition to this basic tissue architecture, the lacrimal gland is highly inundated with trafficking B and T lymphocytes as well as plasma cells.[2]

The lacrimal gland has both the sympathetic as well as parasympathetic innervation.[3] These nerves have a large number of cholinergic fibers and fewer adrenergic fibers. The parasympathetic postganglionic neural cell bodies are found in the pterygopalatine (sphenopalatine) ganglion as well as the ciliary ganglion. Sympathetic fibers arise in the superior cervical ganglion. There is also some sensory innervation of the gland from the trigeminal ganglia.[4]

The lacrimal gland secretes a number of proteins like lysozyme, lactoferrin, lipocalin, and sclgA.[5] The secretion of these proteins is regulated by the nerves and their associated neurotransmitters or neuropeptides.[2] The important receptors present on the lacrimal gland are acetylcholine receptors like muscarinic M3, vasoactive intestinal peptide types I and II and norepinephrine receptors like alpha 1 and beta.[6] Other receptors present are for interacting with neuropeptide Y, adrenocorticotrophic hormone (ACTH) and alpha- melanocyte stimulating hormone (MSH). Since the epithelial cells of the gland are extensively coupled by junctional complexes, secondary messengers like inositol triphosphate can easily diffuse between cells and activate the unstimulated cells too.[2]

The dry eye syndrome

The International Dry Eye Workshop, 2007[1] defined dry eye as:

> ''*Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbances and tears film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of tear film and inflammation of the ocular surface.*''

Dry eye is associated with a high incidence of ocular morbidity. The current prevalence of dry eye in the world is estimated at around 11% to 22%.[7] In the Indian context, these numbers are estimated to be around 18.4–20%.[8,9] These epidemiological numbers are a good indicator of the need for research on dry eye syndrome.

The etiology of DES involves a vicious loop of tear hyperosmolarity, tear film instability and ocular surface inflammation.[10] In addition to this, there is also loss of anti-inflammatory environment within the gland which may happen in cases of low androgen pool. Severe dry eye is also seen in patients of Sjogren's syndrome in which autoantigens are expressed at the surface of the epithelial cells. These cause homing and retention of tissue specific CD4 and CD8 cells, leading to immune-mediated destruction of the acinar and ductal components.

Orbital radiation therapy, which is a commonly used modality in the treatment of oculo-adenexal disorders including malignant tumors, has also been implicated in the development of DES in patients. Despite a rapid evolution in the field of radiotherapy over the past years, a significant number of patients are still seen with acute and chronic ophthalmic complications including severe dry eye.[11,12] Preliminary data from our institute indicate that chronic dry eye develops in over 49% of the patients who undergo external beam radiation therapy for ocular malignancies (unpublished data).

Contact lens wear is yet another condition that may lead to the development of severe dry eye in long-term users. Reduced corneal sensitivity and tear film hyperosmolarity are the probable underlying mechanisms.[1]

The current treatment modalities available for DES are lubricating agents like hydroxymethyl cellulose, solutions containing bicarbonates and potassium, hyposmotic artificial tears and artificial serum. In cases of severe dry eye, therapies such as anti-inflammatory medications (cyclosporin A, corticosteroids), pharmacological tear stimulants like diquafosol, rebamipide, ecabet sodium, pilocarpine etc. have also been used. In certain severe cases, surgical interventions like punctal occlusion and salivary gland auto-transplantation are done to slow down the progress of the condition and minimize detrimental sequale.[13]

On recommendation of the committee on the therapy and management of dry eye, the treatment or management protocol for this condition is now shifting toward employing strategies that would increase the natural production of tears, maintain ocular surface integrity and reduce or elimi-