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TFOS DEWS II pathophysiology report

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ABSTRACT

The TFOS DEWS II Pathophysiology Subcommittee reviewed the mechanisms involved in the initiation and perpetuation of dry eye disease. Its central mechanism is evaporative water loss leading to hyperosmolar tissue damage. Research in human disease and in animal models has shown that this, either directly or by inducing inflammation, causes a loss of both epithelial and goblet cells. The consequent decrease in surface wettability leads to early tear film breakup and amplifies hyperosmolarity via a Vicious Circle. Pain in dry eye is caused by tear hyperosmolarity, loss of lubrication, inflammatory mediators and neurosensory factors, while visual symptoms arise from tear and ocular surface irregularity. Increased friction targets damage to the lids and ocular surface, resulting in characteristic punctate epithelial keratitis, superior limbic keratoconjunctivitis, filamentary keratitis, lid parallel conjunctival folds, and lid wiper epitheliopathy. Hybrid dry eye disease, with features of both aqueous deficiency and increased evaporation, is common and efforts should be made to determine the relative contribution of each form to the total picture. To this end, practical methods are needed to measure tear evaporation in the clinic, and similarly, methods are needed to measure osmolarity at the tissue level across the ocular surface, to better determine the severity of dry eye. Areas for future research include the role of genetic mechanisms in non-Sjögren syndrome dry eye, the targeting of the terminal duct in meibomian gland disease and the influence of gaze dynamics and the closed eye state on tear stability and ocular surface inflammation.

1. Goals

To:

- Summarize current understanding of tear physiology as it relates to dry eye disease (DED).
- Provide an etiological classification of DED.
- Identify the core mechanisms of DED, especially ocular surface hyperosmolarity, tear instability and the inflammatory response.
- Consider the Vicious Circle of DED and chronic DED as a self-perpetuating disease.
- Discuss asymptomatic and symptomatic DED and the basis of DED symptoms.

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- Review the role of environment in precipitating DED in at-risk subjects and influencing DED severity.

2. Definition of dry eye disease

TFOS DEWS II has redefined dry eye as: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (see TFOS DEWS II Definition & Classification Subcommittee report [1221]).

3. Introduction

The purpose of this report is to review our understanding of the pathophysiology of DED, highlighting those advances that have occurred since the TFOS DEWS report [1]. Our general thesis is that DED is initiated by desiccating stress and perpetuated by a Vicious Circle of ocular surface inflammation.

The *raison d'etre* of the eye is sight and the precorneal tear film and the cornea provide the first refractive element of the eye that focuses an image of the visual world upon the retina. To maintain optical quality, the tear film must be constantly replenished by blinking and tear secretion. Without this, the tear film would destabilise and the surface of the eye would be exposed to damaging desiccation. Various mechanisms are in place to achieve homeostasis.

4. Anatomy and physiology of the ocular surface and lacrimal system

4.1. Ocular surface

The ocular surface is covered by a continuous sheet of epithelium, lining the cornea, the anterior globe and tarsi and extending to the mucocutaneous junctions (MCJs) of the lid margins. Hydration of the ocular surface is maintained by the tears, which bathe it continuously and provide an unbroken film over its exposed surface. The tears are secreted chiefly by the lacrimal glands, with additional contributions from the conjunctiva, including the goblet cells and Meibomian glands.

The open eye is constantly subjected to desiccating stress through evaporation of the tears, but is protected from damage by homeostatic mechanisms that regulate tear secretion and distribution in response to signals from the ocular surface. In DED, a failure of these mechanisms leads to a quantitative or qualitative deficiency of tears that typically induces tear film instability, wetting defects and hyperosmolar stress, increased friction and chronic mechanical irritation at the ocular surface. This initiates a chain of inflammatory events and surface damage that characterise the disease.

4.2. Main and accessory lacrimal glands

The main lacrimal gland is a tubule-acinar, serous gland composed primarily of acinar, ductal, and myoepithelial cells, with the acinar cells comprising 80% of the total. It develops by a process of branching, involving reciprocal interactions between the epithelium and surrounding mesenchyme [2,3] to produce a three-dimensional tubular network [4]. In humans, the main gland consists of a larger orbital lobe, and a smaller palpebral lobe that abuts the conjunctival sac. The ducts from the orbital lobe pass through, and join with, those of the palpebral gland, to open into the superior fornix [5], via 6 to 12 orifices [6]. In addition, there are about 40 accessory glands of Krause located in the upper fornix and 6 to 8 in the lower fornix. The accessory lacrimal glands of Wolfring, located in the upper (2–5 glands) and lower (1–3 glands) lids, are slightly larger than those of Krause. The accessory lacrimal glands are tubular glands which do not contain acini in humans [7], but do in rabbits [8]. The accessory glands constitute about 10% of the total lacrimal tissue mass [9] and are innervated similarly to the main gland [10]. They are therefore assumed to respond in a similar way to reflex stimulation.

4.2.1. Resident immune cells of the lacrimal gland

The lacrimal gland is richly supplied by immune cells that occupy the interstitial space. They include: plasma cells, B and T cells, dendritic cells, macrophages, bone marrow-derived monocytes, and mast cells [11] (Table 1).

Plasma cells predominate (53.9% of the total), mainly immunoglobulin (Ig) A+ and with a few IgG+, IgM + or IgD+. The IgA + cells synthesize and secrete IgA, which is transported into acinar and ductal cells, combined with J-piece and secretory component (SC) and secreted as dimeric, secretory IgA (sIgA) [12,13]. A similar event may occur in the conjunctiva and in other Eye-Associated Lymphoid Tissues (EALT) [14].

T cells are the next most common cell, (40.3% of total), dispersed with plasma cells in the interstitium, in follicles and aggregates and occasionally between acinar cells. T cell aggregates are typically related to intra-lobular ducts. Overall, T suppressor/cytotoxic cells (T8) are more numerous than T helper cells (T4), distributed almost equally between acini, ducts and interstitium. The T4/T8 ratio is 0.26 in the interstitium. However, T4 cells predominate in follicles and lymphocytic aggregates. Dendritic cells, macrophages, bone marrow-derived monocytes and mast cells are also present.

B-cells are found exclusively in the centre of primary follicles and aggregates and in solitary, secondary follicles, surrounded by T helper cells and a lesser number of suppressor/cytotoxic cells. They are not found in the interstitium. They make up 5.7% of the mononuclear population. B-cells and the dendritic cells of follicles and aggregates express human leukocyte antigen D-related (HLA-DR) as do duct lining cells and the vascular endothelium. Macrophages and dendritic cells are uncommon.

4.2.2. Regulation of lacrimal secretion

The acinar cells are arranged in lobules around a central lumen, with tight junctions surrounding each cell on the apical (luminal) side [12,15]. This configuration permits the unidirectional, basal-to-apical, secretion of water, electrolytes, proteins and mucins [12,15]. The basal portion of the cell contains a large nucleus, rough endoplasmic reticulum, mitochondria, and Golgi apparatus while the apical portion is filled with secretory granules [12,15]. The acinar cells synthesize, store, and secrete proteins and mucins in response to neural and hormonal stimuli [13,15]. They also secrete electrolytes and water. Many of the proteins secreted have either growth factor or bactericidal properties, which are crucial to the health of the ocular surface. Several mucins, both secreted as well as membrane-bound have been detected in the lacrimal gland including MUC1, MUC4, MUC5B, MUC5Ac, MUC6, MUC7 and MUC16 [16–18]. Some of them perform local roles but otherwise their functions are not known.

Like the acinar cells, the duct cells are polarized by apically located tight junctions [12]. Importantly, the ductal cells modify the primary fluid secreted by the acinar cells by absorbing or secreting water and electrolytes [19,20]. The duct cells secrete a KCl-rich solution so that the finally secreted lacrimal gland fluid is rich in K^+ ions. It has been estimated that as much as 30% of the volume of