Editorial

What drives Meibomian gland disease? ¿Qué causa la enfermedad de las glándulas de Meibomio?

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The lacrimal film, the glands and cells that produce it, the ocular surface, eyelids and motor nerves that connect them are together defined as the lacrimal functional unit. Any disorder or damage of any element of this functional unit could de-stabilize the lacrimal film and produce the dry eye syndrome (DES). The International Dry Eye Workshop (DEWS) has defined DES as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface (DEWS 2007). DES is a highly prevalent ocular pathology with severe consequences for patients, ranging from ocular discomfort to visual dysfunction and corneal ulcer in severe cases. Epidemiological study data indicate that DES is a common disease, particularly in the elderly population, which affects up to 20% of adults over 45 and is one of the most frequent reasons for attending ophthalmology practices. Even though DES can be due to a deficiency in the aqueous component of tears (dry eye due to aqueous deficiency), it is more frequently associated with evaporation of water from tears ( evaporative dry eye).

Meibomian gland dysfunction (MGD), a term which describes a diffuse anomaly of the Meibomian glands, is considered to be the most common cause of DES, although it can also account for eyelid inflammation which may not express as typical DES. At present it is accepted in ophthalmology that the Meibomian gland is a key component in DES etiology and contributes to the evaporative condition of the lacrimal film. At presence, 3 forms of MGD are recognized: (i) hyosecretory, (ii) hyposecretory, and (iii) MGD obstructive, the latter being the most common form. On the basis of clinic and animal studies at present it is believed that obstructive MGD is mainly caused by an obstruction of the terminal duct due to hyperkeratinization of the duct epithelium together with higher viscosity of the meibum which initially obstructs the Meibomian gland orifice followed by cystic dilatation of the duct and diffuse atrophy of the acini. However, MGD can also facilitate bacterial growth on the edges of the eyelids and promote inflammation of the adjacent conjunctiva. The development of MGD has been associated to several risk factors including aging, androgenic deficiency, treatment with isotretinoin and possibly post-menopause treatment with estrogens. MGD diminishes meibum availability in the eyelid edges and the lacrimal film. The consequence of lipids insufficiency could be increased evaporation, hyperosmolarity and lacrimal film instability, as well as higher bacterial development on eyelid edges, evaporative dry eye and ocular surface inflammation and damage. However, the underlying molecular mechanisms involved in MGD pathogenesis are unknown. This lack of information has prevented the development of safe and efficient therapies for treating said dysfunction. In general, MGD is a highly important disorder which is probably underestimated and is most likely to be the most frequent cause of dry eye disease.

Accordingly, the question is: which is the physiopathology underlying obstructive MGD? It is known that a number of factors contribute to DES physiopathology including...
topically administered drugs/preservatives, allergies, the use of contact lenses, viral/bacterial conjunctivitis, neurotrophic factors, LASIK/refractive surgery, ocular surgery, systemic drugs, Sjögrens syndrome, other self-immune diseases, sexual steroids/hormonal imbalance and blepharitis/MDG as well as chalasis and irregularities of the eyelid edges. All this can produce lacrimal film instability/imbalance with rapid lacrimal film rupture after blinking, caused when the interaction of lacrimal film components are affected by diminished lacrimal secretion, delays in clearing or tear composition alterations. In turn, this produces local dryness and hyperosmolarity, a key stage in the vicious circle of DES physiopathology. Lacrimal hyperosmolarity produces morphological changes such as apoptosis of conjunctival and corneal cells as well as activating an inflammatory cascade which contributes to increased cell death, including the loss of mucine-producing sickle cells. This exacerbates lacrimal film instability and contributes to the cycle of events that perpetuate DES.

Recent research has demonstrated that MGD brings about multiple changes in the genetic expression of the Meibomium gland. The most overexpressed genes are those which encode small proline-rich proteins and calcium-binding S100 proteins, which in turn involve genes that participate in keratinization as well as innate immune response. These results strongly support the hypothesis that keratinization plays an important role in MGD pathogeny. In this regard, the fact that many proteins that are essential for epidermis differentiation and keratinization are encoded by genes grouped in the human chromosome 1q21 region is of great interest. Said genes comprise the “epidermal differentiation complex” (EDC) which is divided in common protein and gene structures in 3 genetic families: (i) precursors of keratinized cellular envelope, (ii) S100A, and (iii) S100 merged genes. Many proteins of these families participate in skin differentiation and keratinization but are also involved in innate immune defense and belong to the antimicrobial peptide group. On the ocular surface, one of these proteins is psoriasis (S100A7) which overexpresses under inflammatory conditions and also expresses in Meibomium gland/meibocyte cells. The expression of EDC proteins is genetically regulated in a specific tissue through a combination of transcription factors, of which Klf4, Ghrh3 and Arnt are essential. Its disappearance in rats is deadly. The importance of EDC is increasingly enhanced by human diseases: filagrin gene mutations are the biggest risk factor for atopic dermatitis and asthma associated to atopic dermatitis as well as defective formation of keratinized cellular envelopes caused by transglutaminase 1 deficiency, which generates a potentially lethal laminar ichthyosis.

In summary, MGD is accompanied by multiple changes in the genetic expression of Meibomium glands. The nature of said alterations mainly includes EDC gene regulation, involved in inflammatory response, epidermis development and innate immunological response. Accordingly, in MGD physiopathology there seems to be a clear correlation between the induction of epidemic differentiation and keratinization on the one hand and epithelial induction of various antimicrobial peptides on the other, which requires verification and additional clarification.

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**References**