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Age-Related Dry Eye Lactoferrin and Lactobionic Acid

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Abstract
Dry eye is the most prominent pathology among those involving the ocular surface: a decrease of the aqueous (less frequent) or the lipid (more frequent) component of the tear film is the cause of the diminished stability of tears that is observed in this pathology. Dry eye shows a clear distribution linked to both sex (being more frequent among women) and age (increasing with aging). Therefore, specific treatments taking into account the etiology of the disease would be desired. The role of lactoferrin and its functional mimetic lactobionic acid are reported here as a possible remedy for age-related dry eye.

Eye Dryness (Keratoconjunctivitis Sicca)

The ocular surface is made up of the epithelial cells of the cornea and the conjunctiva and the tear film in which they are bathed and that protects them thanks to its mechanical (lubricating) and metabolic (nourishment) properties. The tear film contains 3 interconnected layers: the mucin layer next to the epithelial surface, the aqueous layer on top of it, and the lipid layer as the outermost one, preventing excessive evaporation of tears. If any of these 3 layers becomes deficient, the epithelial cells are damaged (by desiccation and by increased friction due to more frequent blinking on a dry surface) and an inflammatory reaction starts, with production of inflammatory mediators that can be found in the tear film and the tissues themselves, further damaging the epithelial layers and starting a vicious cycle that aggravates the pathology if not efficiently interrupted.

Current Treatments of Dry Eye

It is nowadays widely recognized that eye dryness is a multifactorial pathology finally leading to tear film insufficiency and signs and/or symptoms of ocular surface disease (OSD). Therefore, treatment should be tailored to each patient trying to target the specific mechanisms involved in her/his peculiar disease [1, 2]. Inflammation is often a key driving mechanism in many cases of OSD,

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and therefore topical antinflammatory drugs (corticosteroids or non-steroidal antinflammatory drugs) are present in the market to treat this aspect of the pathology [3]. Cyclosporine can also be used to exploit its immune-modulating activity [4]. Antibiotics with antinflammatory action (such as azithromycin) may be used to treat Meibomian Gland Disease, often due to infective blepharitis [5]. Vitamins and antioxidants have been used to tackle the oxidative stress side of the disease [6]. Free amino-acids added to a lubricating agent such as hyaluronic acid improved its ability to attenuate signs and symptoms of dry eye [7]. Essential fatty acids (omega 3 and 6) may have antinflammatory and immunemodulatory activities, with a beneficial effect on dry eye pathology [8]. Hormone replacement therapy with androgens or estrogens take into account the influence of hormones on the homeostasis of the integrated system ocular surface/lacrimal glands [9]. Tear stimulating drugs (mucin secretagogues, muscarinic receptor agonists, stimulating exocrine glands activity) such as rebamipide can be used to try and increase the production of tear film components such as the mucous and the aqueous layers [10]. Homologous or heterologous serum derivatives are used as biological tear substitutes with promising results [11]. Relatively few studies have addressed the development of specific products for age related dry eye [12], which however is on the increase, due to the increasing life expectancy, at least in the western world.

Endogenous and Iatrogenic Causes of Age-Related Dry Eye

Aging is one of the most frequent endogenous causes of dry eye. About 5–30% of the elderly show signs of eye dryness, the reported frequency being 8.4% below 60 years of age, 15% between 70 and 79 years, and 20% for individuals over 80 years; women, as expected, show a higher prevalence in all age groups [13, 14]. The higher risk of developing dry eye in the elderly may be due to several factors affecting the different layers of the tear film. The secretory function of the lacrimal gland, producing the aqueous component of the tear film, is regulated by androgens, the production of which is known to change with aging, more for women than for men [15]. Therefore, dry eye caused by lacrimal gland dysfunction is more common in females [16]. A higher incidence of autoimmune diseases (Sjogren syndrome, and rheumatoid arthritis) correlates with aging, as well as a decreased corneal sensitivity, both causing a decrease in tear production [17]. Deficient tear production can also be caused by a chronic use of systemic and topic medications, which in the elderly accumulate over time, especially for those affected by glaucoma [18].

Mucin-producing goblet cells decrease their function with aging [19], and conjunctival cells become more susceptible to apoptosis [20]. This condition may lead to a decreased wettability of the ocular surface, which rapidly becomes dry, and to a diffuse damage of epithelial cells, finally leading to symptomatic eye dryness.

Tear film stability is also influenced by aging. Abnormal eye lid positioning (laxity, floppy eyelid syndrome, retraction and lagophthalmos), together with meibomian gland dysfunction, increase the rate of tear film evaporation, decreasing tear film breakup time. In fact, dry eye syndrome can be seen in as many as 50–70% of patients with eyelid malpositioning [21]. A dysfunction of the meibomian glands (producing the lipid layer of the tear film) is also observed with andropause or menopause and the corresponding alteration of sex hormones, leading to a thinning of the tear lipid layer and increased tear evaporation [22–24]. Other hormonal factors that may lead to eye dryness include the Growth Hormone/IGF-1 axis. Their secretion declines over time, until only low levels can be detected in individuals aged over 60 years [25]. This results in the inhibition of the Foxo1 gene, which in turn leads to decreased proliferation and lipogenesis in meibomian gland cells, increased apoptosis and delayed turnover [26].

Corneal sensitivity changes with aging, and in some cases a decreased sensitivity has been reported [27] with the expected result of a reduced feedback stimulating lacrimal gland secretion, while in other cases hypersensitivity has been noted [28]. In either case, the morphology of corneal nerves (a bead-like transformation) becomes altered with dry eye, most likely as a consequence of the inflammatory state present in the cornea, and the discomfort of the patient is increased [29].

Neurodegenerative diseases show an increased incidence with advancing age, and may favor the insurgence of dry eye. In Parkinson's patients, a lower blink rate and a decreased corneal sensitivity have been reported, which may lead to increased evaporation and reduced tear secretion [30].

Protein content in the tear film may also change with ageing and dry eye, and very often a decrease in lactoferrin (Lf) and lysozyme is observed [31, 32].

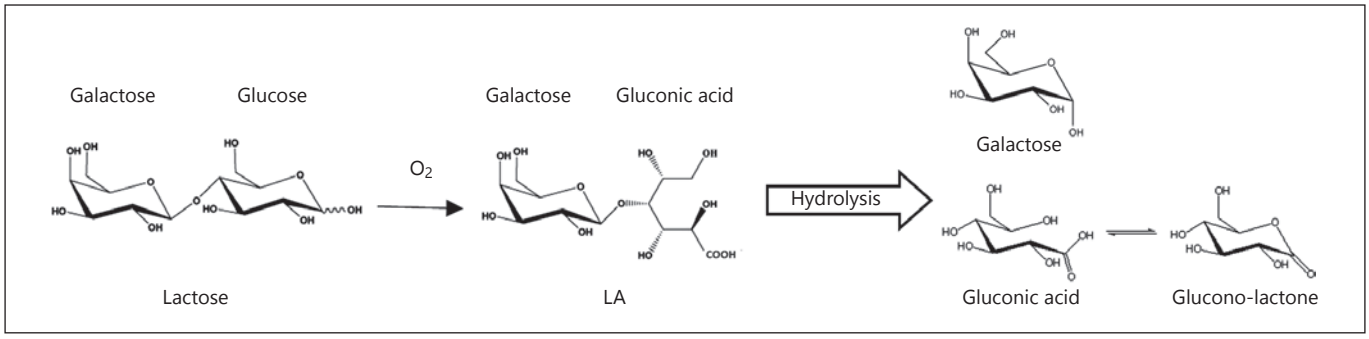

Fig. 1. Biosynthesis of lactobionic acid (LA). The LA molecule is made of a sugar (galactose) bound by an ether link to a poly-hydroxy acid (gluconic acid). LA is formed via oxidation of lactose (the milk sugar) and it can be enzymatically degraded to its constituents (galactose and gluconic acid), which are both molecules normally present in cells, so that their tolerability is high.

The Role of Lactoferrin in the Tear Film

The ocular surface is constantly exposed to the external environment, so that several bacterial strains establish a symbiotic relationship with it, similarly to what happens in the intestine. However, ocular infections are not as common as could be expected from this permanent exposure. In fact, ocular pathogens in order to succeed have to compete with the endogenous bacterial strains of the ocular surface [33], and escape from the defense proteins present in the tear film [34]. The main proteins of this class that are synthesized by cells residing in the eye are Lf, lysozyme, immunoglobulin-A and tear lipocalins [34]. Lacrimation and a regular turnover of the tear film are critical to reintegrate the defense proteins in order to efficiently protect the ocular surface.

Tear Lf is mostly secreted by the main lacrimal gland [35], although both epithelial cells of the ocular surface [36] and meibomian glands [37] can also contribute to its final tear concentration. Lf is a glycoprotein belonging to the transferrin family of proteins, with a molecular mass of 80 kDa. Structurally, it contains two lobes joined by a peptide bridge that confers some flexibility to the molecule; each lobe has the capability of chelating one ferric ion (Fe^{+3}), so that Lf forms complexes with ferric ions in the ratio 1:2.

In the tear film, Lf has multiple roles: antinflammatory, antioxidant and antimicrobic.

The antinflammatory activity depends on Lf interaction with natural and induced immunity, and its ability to regulate inflammatory cytokine expression with the overall result of reducing inflammation [38]. The antioxidant and antimicrobial activities are linked to the iron-chelating ability of Lf, which prevents the formation of iron-dependent hydroxyl radicals that can be generated during an inflammatory response and by microbial infections [38, 39]. Moreover, since iron is a critical co-factor for bacterial growth and proliferation, the subtraction of iron by Lf has a limiting effect on bacterial survival. In addition, Lf also inhibits biofilm formation, and thus may play a role in protecting contact lens surfaces from microbic colonization [38].

Lf represents around 25% of tear proteins, with an average concentration in healthy subjects of 1.42 mg/mL [40]. Its concentration decreases with prolonged closure of the eyelids, as happens during sleep [41], when protection from external insults is not necessary. Ageing and some eye pathologies such as dry eye (Sjogren and non-Sjogren), keratitis and conjunctivitis of different etiologies result in a decrease of tear Lf [42], so that these individuals become more susceptible to ocular infections [43].

In view of the relevant protective role that tear Lf has on the ocular surface, and its decrease with ageing and disease, several attempts have been made to replenish Lf in tears, however, so far these have not been successful since no topical treatment with exogenous Lf is available. However, oral supplementation of Lf has had some effect in attenuating dry eye induced by cataract surgery [44]. A possible alternative would be to find other molecules with an activity similar to that of Lf.

Lactobionic Acid: A Functional Mimetic of Lactoferrin?

The molecule of lactobionic acid (LA) is made by a sugar (galactose) bound through an ether link to a poly-hydroxy acid (gluconic acid; Fig. 1). More generally, bi-

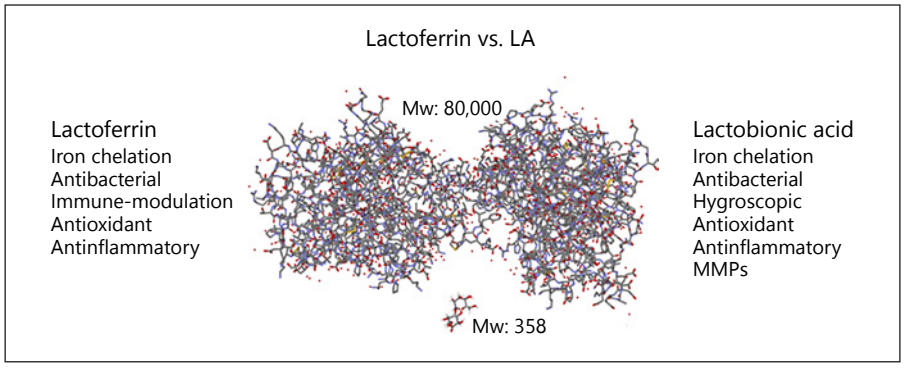

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Fig. 2. Molecular structure and biological functions of Lf compared to LA. Lactoferrin (Mw: 80,000 Da) is a critical component in tears with important biological activities, many of which are in common (in bold) with LA (Mw: 358 Da). LA could be used in artificial tears as a functional mimetic of Lf and a protective agent on the ocular surface. Lf, lactoferrin; LA, lactobionic acid; Mw, molecular weight; MMPs, matrix-metalloproteinases.

onic acids are those formed by a poly-hydroxy acid and a sugar, where the "bi" indicates the presence of two moieties in the molecule. LA is formed via oxidation of lactose (the milk sugar; Fig. 1). In the skin, it can be enzymatically degraded to its constituents (galactose and gluconic acid), which are both molecules normally present in cells, so that their tolerability is quite high.

Thanks to the many hydroxyl groups, LA has a very high water retention capacity and moisturizing ability [45]. Its antioxidant property mainly derives from its iron-chelating capability. LA forms 1:1 chelating complexes with ferric ions [46]. Ferric ions may generate free hydroxyl radicals: iron chelation prevents this chemical reaction [47]. Therefore, these 2 abilities, antioxidant and hygroscopic, make LA an ideal molecule for anti-ageing cosmetic treatment [48] and for transplant organ preservation [49]. Moreover, since iron is a necessary metabolite for bacterial growth [50], it could be expected that LA, similarly to Lf, has antibacterial effects [51]. LA is even a more efficient iron chelator than Lf on a mass basis, since – given the much lower mw of LA (358 Da) with respect to Lf (80 kDa) – 1 mg of LA can chelate 112 times more iron than 1 mg of Lf, despite the fact that on a molar basis Lf chelates twice the amount of iron with respect to LA. Therefore, considering a physiological concentration of tear Lf of 1.4 mg/mL, a tear concentration of at least 0.21 mg/mL of LA would be enough to re-establish the iron chelating capability of Lf-depleted tears. Considering that about 5% of an artificial tear remains on the ocular surface after instillation, an LA concentration of at least 4 mg/mL would be advisable to reintegrate the missing Lf in tears of dry eye patients.

Finally, LA – similarly to other bionic acids – inhibits matrix-metalloproteinase (MMP) activity [52]. MMPs are enzymes that degrade collagen in the extracellular matrix as part of the natural process of collagen turnover. With ageing, and in cases of oxidative stress further to inflammatory events, there is an upregulation of MMPs and consequent collagen degradation [53]. Blocking MMP activity can help preserve existing collagen and maintain firmer and tighter skin. More specifically, after cutaneous administration of LA as a gel, the epidermis looked thicker and a strong inhibition of epidermal MMP9 was visible, together with an enhanced presence of hygroscopic glycosaminoglycans in the dermis and a general improvement of skin elasticity and smoothness [54].

Animal Models to Address Dry Eye

Dry eye is a dynamic process involving the several structures forming the lacrimal functional unit, as originally described [55], and as such is almost impossible to reproduce in vitro. Therefore, several in vivo animal models have been developed in different species over time, to address the specific events leading to dry eye, either of the evaporative or secretory type [56]. Other models have rather been focused on the inflammatory and immune-mediated processes behind the development of dry eye [57], thus allowing to study the related processes and therapeutic approaches. However, to our knowledge, no animal models have been described to date, in which Lf deficiency is a major contributor to OSD and would thus allow to specifically address the efficacy of a Lf functional mimetic such as LA. The major source of tear Lf is the lacrimal gland, although both corneal and conjunctival cells in mammals [36, 58] are known to produce detectable amounts of Lf.

It would be interesting to see the effects of a conditional knockout of Lf in these tissues on the pathogenesis

of dry eye, and – similarly – to see whether there are compounds that, given topically, may stimulate the production of endogenous Lf.

Conclusions

In conclusion, it is known that ageing results in the progressive impairment of several organs and tissues, including the eye and the ocular surface. Palliative medicine (there is no cure for ageing as yet) can try to replace, at best, those components that become altered with ageing and, in so doing, reduce the increasing risk of developing pathological degenerations.

Lf has been identified as one of the critical components in tears that becomes deficient with ageing and with progressive eye dryness, leaving the ocular surface at higher risk of infection. We propose here that LA could be used in artificial tears as a functional mimetic of Lf and a protective agent on the ocular surface (Fig. 2). In fact, it is endowed with hygroscopic, iron-chelating, anti-oxidant and anti-inflammatory properties that make it an ideal candidate to counteract the effects of ageing on the ocular surface.

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