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Review

Function of meibomian gland: Contribution of proteins

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ABSTRACT

The meibomian gland is the major contributor to the tear film lipid layer. It is generally accepted that meibomian gland secretions, i.e, meibum, play a critical role in the homeostasis of the tear film. Lipid components of meibum and their structure, as well as functions were intensively studied. However, the proteins from meibum have not attracted enough attention. This review summarizes current knowledge about protein components of the meibum, particularly their function on tear film and ocular surface, and changes in the proteins during meibomian gland dysfunction (MGD).

Contents

1. Introduction

Meibomian glands are modified holocrine sebaceous glands that are embedded in the tarsal plate of both the upper and the lower

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eyelids (Jester et al., 1981). The meibomian gland secretions, i.e, meibum, consist of a complex mixture of various polar and nonpolar lipids containing cholesterol, wax esters, diesters, triacylglycerol, free cholesterol, free fatty acids, and phospholipids (Green-Church et al., 2011). The meibum spreads onto the tear film and functions to reduce the evaporation of the aqueous component, smoothen the corneal surface, and form a barrier to protect the eye from microbial agents and organic matter such as dust and pollen (Wang et al., 2016a; Den et al., 2006; Holly and Lemp, 1977).

In the pathological stage, meibomian gland can undergo functional and structural changes, leading to meibomian gland dysfunction (MGD). Although the precise aetiology and pathophysiology of MGD remains elusive, in 2011 the International Workshop on MGD proposed a definition for MGD as "a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease" (Nichols et al., 2011).

It is well accepted that MGD is the most common cause of evaporative dry eye (Schaumberg et al., 2011). MGD is found even in situations previously considered to be the primary aqueous deficient dry eye (Lemp et al., 2013). Therefore, MGD may also have some association with this condition. It is commonly believed that lipid plays a critical role in the homeostasis of tear film. MGD related dry eye is due to the reduction of lipid secretion from meibomian glands which induce tear film instability, hyper-evaporation of aqueous tear and entry into the vicious circle of dry eye.

Recently, there are emerging evidences showing that rather than just lipid components, meibum also contains different proteins. How these proteins contribute to the homeostasis of tear film and the ocular surface is attracting more attention. In this review, we summarize our current knowledge about the protein components in meibomian gland secretion, analyze possible functions of these proteins on the homeostasis of tear film and ocular surface, and propose future research direction in this field.

2. Meibum protein components

The tear film is packed with numerous proteins whose major sources are corneal epithelial cells, goblet cells, lacrimal gland, mebomian gland, and blood vessels. Proteomics analysis of human tears in healthy subjects and dry eye patients has been intensively performed in recent years (Srinivasan et al., 2012) (Li et al., 2014; Aluru et al., 2012). However, there are very few studies describing the identity of proteins in meibum. Infrared spectrum and nuclear magnetic resonance spectroscopy indicated the presence of protein components in the meibum (Borchman et al., 2011, 2010, 2012). Till now, the only proteomic analysis of human meibomain gland secretions was done by Tsai et al. (2006). They identified more than 90 proteins in human meibum. Keratins (K1, 5, 6, 7, 9, 10, 13, 16), lactoferrin, lipophillins, lipocalins, phospholipid transfer proteins, surfactant proteins (SP-B,SP-C), proteoglycans, cytochrome *c*, farnesoid X laminin a-3 chain, lysozyme c are enumerated to be the major protein components of meibum (Tsai et al., 2006; Glasgow et al., 1995; Jauhiainen et al., 2005). The major categories of meibum proteins are listed in Table 1.

Among the listed proteins detected in meibum, keratins are most commonly studied in the ocular surface. Keratin 10 was detected in both normal and MGD meibum and considered to be secreted from keratinized duct epithelial cells (Igor et al., 2014). Keratin7 and Keratin13 are expressed in the meibomian acinar cells. Due to non nuclear protein co-expression with keratin positive expression, the keratins in meibum were considered to be derived from dead/lysed cells (Ashraf et al., 2011). They most likely originate from the shedding of keratinized epithelial cells lining the meibomian gland ducts (Ong et al., 1991). It has been shown that the levels of keratin in meibum increase up to 10% in MGD patients. Keratin may have a role in obstructing secretion of meibum from the ducts due to hyperkeratinization (Ong et al., 1991). Recent studies observed that keratin mixes into the lipid layer of the tear film, and likely destabilizes the lipid layer in vitro (Borchman et al., 2010; Palaniappan et al., 2013). Thus, excess concentrations of keratin in patients with MGD may disrupt the normal structure of the meibomian lipid film, which may reduce tear break-up time (Igor et al., 2014). However, it is not known in vivo if the increased keratin affects changes in the function of the tear film lipid layer.

3. Function of meibum proteins

Although Tsai et al. described the functions of some proteins in the meibum (Tsai et al., 2006), the function of most of the proteins on the tear film and ocular surface was not well studied. In this review, we have updated the functions of these proteins and focused on their role in maintaining the ocular surface integrity, and have proposed their potential functions based on studies in other organs or tissues (Table 2). We classified these proteins into three major categories according to their function.

3.1. Proteins related to ocular surface epithelial protection

Basic proline rich protein 1 was mostly found in human saliva. It could provide protection against dietary tannins which could damage the gastrointestinal epithelium and mucosa (Cai, 2006; Shimada, 2006). Actotransferrin, also named as lactoferrin, is an iron-binding protein, which can reduce the availability of iron necessary for microbial growth and survival. It may stabilize the tear film, avoid excessive tear evaporation, ocular surface desiccation and protect eyes from oxidative stress (Pastori et al., 2015). It can promote wound healing and suppress inflammatory cytokine IL-1 (Pattamatta et al., 2013; Ashby et al., 2011). The amount of lactoferrin was found reduced in keratoconus tears (Balasubramanian et al., 2012). Cytochrome C is related to caspase-dependent apoptosis, it could have been released from mitochondria of the conjunctival cells which is evident in BAK induced dry eye model (Clouzeau et al., 2012).

Proteoglycan 4 (PRG4, lubricin) mRNA was detected in human meibomian gland epithelial cells and expressed in the full thickness of the corneal and conjunctival epithelium. PRG4 knockout mice demonstrated significant corneal fluorescein staining, suggesting increased corneal damage (Samsom et al., 2014). PRG4 could be a protectant by reducing friction at the human cornea-eyelid, cornea-conjunctiva and human cornea-polydimethylsiloxane (PDMS) interfaces. Conjunctival changes may have occurred as a result of PRG4 absence and limited the efficacy of lubricin (Schmidt et al., 2013). In clinical trials, conjunctival erythema was significantly reduced by application of lubricin eye drops to the biointerfaces. Loss or downregulation of lubricin likely increases shear stress at the ocular surface, which, in turn may lead to inflammation, stimulation of corneal nerves, and accumulation of inflammatory mediators (Morrison et al., 2012).

Forkhead related protein is involved in normal corneal development. Increase in its expression levels may alter corneal epithelial thickness (Lehmann et al., 2003). Farnesoid X activated receptor is also expressed in the basal cells of corneal epithelium (Higashiyama et al., 2008), it can accelerate epidermal barrier development. TrkC tyrosine kinase (TrkC) was noted in the suprabasal layers of corneal and limbal epithelia (Touhami et al., 2002). Ellis Van Creveld Syndrome 2 protein (EVC2) maintains the stemness of the dental mesenchymal stem cells. Loss of EVC2 could lead