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Development of occupational ophthalmology: from dry eye syndrome to artificial tears

Oktay Gasymov*, Azad Abdurahimov

Institute of Biophysics, Ministry of Science and Education of the Republic of Azerbaijan, 117 Academician Zahid Khalilov Str., Baku, AZ1141, Azerbaijan

***For correspondence:** oktaygasimov@gmail.com*
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In this short review, we convey the history of occupational ophthalmology in the former Soviet Union that has been developed under the supervision of academician Zarifa Aliyeva. Research initiated by acad. Z. Aliyeva has provided the foundation for the new discipline of "occupational ophthalmology". Occupational ophthalmology, as a part of occupational medicine, has a long history of development. The first studies and implementation of occupational ophthalmology in the world started in about the fourth decade of the twentieth century. Particular aspects of occupational ophthalmology depend on the specifics of the particular industry. Here we describe dry eye syndrome that has been diagnosed in millions of people worldwide. Dry eye syndrome is described as one of the consequences of certain occupations, particularly prolonged work with a computer. The structure of the ocular surface of the human eye is described for a better understanding of the consequences of a prolonged dry eye condition. Experimental data suggest that tears play the principal role in maintaining and protecting ocular surface health.

Keywords: *Occupational ophthalmology, human cornea structure, tear film, dry eye syndrome*

History of occupational ophthalmology. For a long time, not much attention was paid to the specificities of human eye diseases developed in various professional activities. The term "occupational ophthalmology" was first coined by Dr. Kuhn in 1946 (Kuhn, 1946). Various environmental conditions associated with the particular workplace (occupation) were recognized as risk factors for different diseases. The eye problems developed in various areas of the industry are multifactoral and very complicated. This situation set the foundation for the development of a new academic discipline-occupational ophthalmology. It was immediately clear that industry-eye physician collaboration is pivotal for sustained progress in preventing eye injuries.

In the former Soviet Union acad. Zarifa Aliyeva first recognized the importance of the development of occupational ophthalmology. For the first time, in 1978 she established a laboratory of "occupational pathology of visual organ" in the Baku plant of domestic air conditioners. The workers exposed to styrene and tetrachlorethylene vapors were identified and a specific therapy was developed for them. This collaboration with industry was very important in creating safe and healthy workplace conditions for the workers of the Baku plant of domestic air conditioners. Academician Z.Aliyeva not only treated the worker exposed to toxic environments but also optimized the workplace to prevent health risk conditions. Thus, a new discipline of "occupational ophthalmology" was founded by acad. Z.Aliyeva. Now, "occupational ophthalmology" is part of "occupational medicine" that covers almost all aspects of human health issues.

Acad. Z.Aliyeva was also among the first ophthalmologist who realized the importance of tears to keep the eye surface healthy. Her fundamental book "Physiology of tear secretion"

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published in 1983 still has a great scientific value (Sultanov and Aliyeva, 1983). The anatomy and physiology of the main and accessory lacrimal glands are described in great detail. Of course, last 40 years a lot of progress has been made in this direction. But the main idea still highlights the importance of healthy tears to prevent many eye surface diseases including dry eye syndrome.

Origin of dry eye syndrome.

In this review, we present a summary of an up-to-date understanding of human tears compositions and functions to keep the ocular surface in healthy conditions. Special emphasis will be given to dry eye conditions that can be the result of various disorders.

It is widely accepted to describe human tear film with a layered structure (Fig. 1). The main functions of the tears are to keep the cornea wet (lubricated), prevent various infections, and provide nutrition to the cornea that lacks blood vessels (Sridhar, 2018). The average diameter and thickness of the human cornea are ~ 11 mm and 0.6 mm, respectively. The outermost part of the cornea is composed of epithelial cells that have about 50 mm thickness. The cornea epithelial cells are constantly renewed and have a lifespan of about 7-10 days. Epithelial cells are connected to the stroma via Bowman's layer (Fig. 2). The epithelial cells of the normal cornea have a five-layered structure (DelMonte and Kim, 2011) and are classified into three types of cells: basal layer (the innermost layer), wing cells and superficial cells (the outermost layer) (Fig. 3).

During the epithelial cell progression, the basal cell layer moves toward the upper part while transforming into a wing and then superficial cells. Superficial cells develop microvilli that produce transmembrane mucins, such as MUC1, MUC4, and MUC16 (Gipson, 2004; Govindarajan, Gipson, 2010). This cell-attached mucin layer keeps the cornea surface wet, and lubricated and provides a mechanical barrier to pathogens and other exogenous particles. The corneal stroma is transparent and its central part lacks blood vessels. Transparency of the stroma results from the particular organization of its constituents, stromal fibers and extracellular matrix (ECM).

Corneal fibrils of the stroma are mainly composed of collagen Type I. A much smaller amount of collagen Type VI and XII are also found in the stroma (Sridhar, 2018). Endothelial cells form a single layer and positioned innermost part of the cornea (Figure 3).

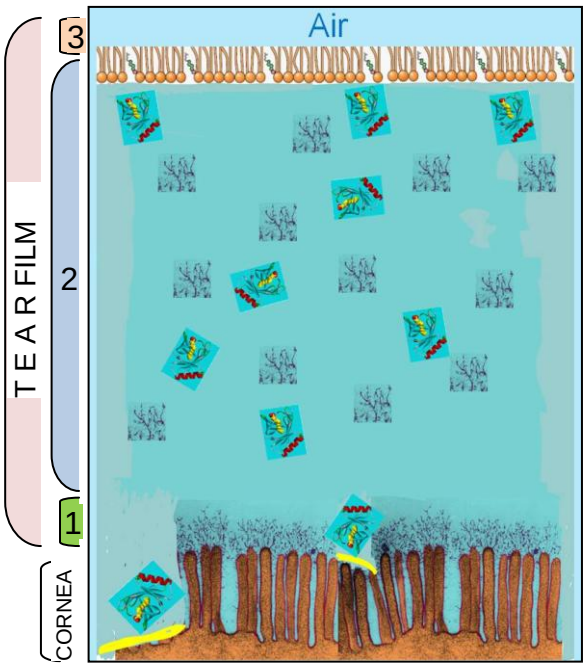

Fig. 1. Tear film of the human ocular surface. Micro-projections from the corneal surface are microvilli. Transmembrane mucins (1), like MUC1, MUC4, and MUC16, cover the apical surface of the microvilli and are considered the innermost 1st layer. The aqueous layer (2) of the tears is made of electrolytes, various types of peptides and proteins, and soluble mucins, such as MUC5 and MUC7. The outermost layer (3) of the tear film is the lipid layer composed of various phospholipids, fatty acids, cholesteryl esters, triglycerides, etc.

The main function of the endothelial layer is to pump water out of the cornea to keep its normal hydration (Waring et al., 1982). Aquaporins, water channel proteins of the endothelium, provide pump functions (Verkman et al., 2008). A damaged endothelial layer does not sufficiently pump water out of the cornea and, therefore, the cornea may swell resulting in a disease called bullous keratopathy.

The thickness of the stroma that provides mechanical properties of the cornea is also essential to vision. In some conditions, a stoma is getting thinner and the cornea gradually bulges outward to take a cone shape. This disorder is

called keratoconus and causes blurred vision. The cornea surface is covered by tear film which is made of three layers (Fig. 1).

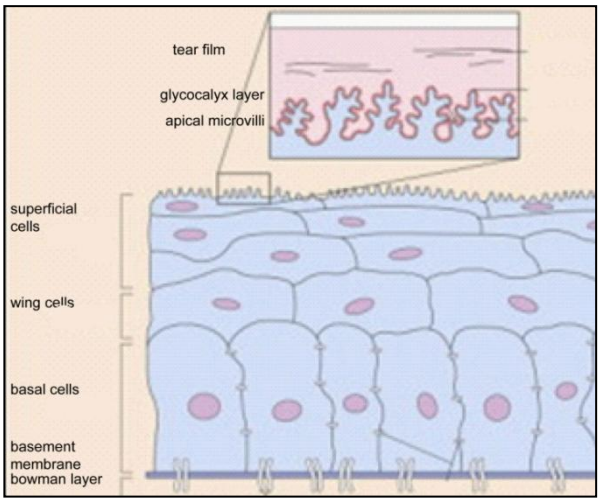

Fig. 2. Details of the epithelial layer of the human cornea.

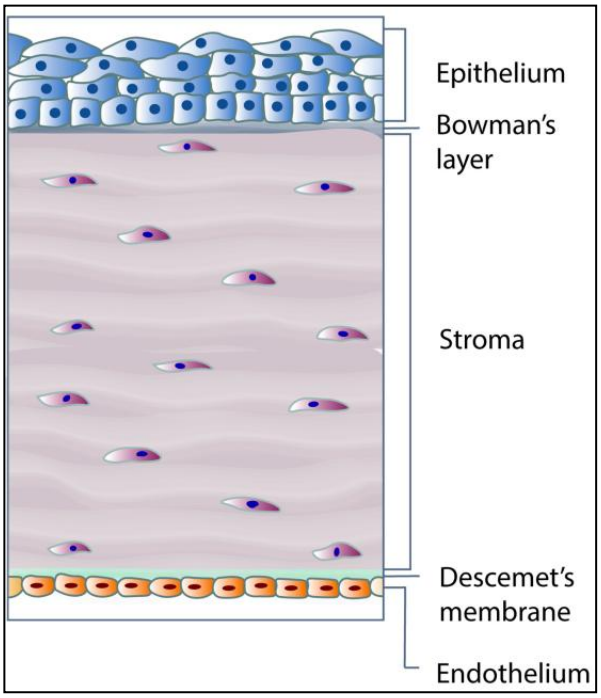

Fig. 3. Structure of human cornea.

As mentioned above, the innermost layer of the tear film is the mucin layer composed of transmembrane mucins (MUC1, MUC4 and MUC16) located at glycocalyx (Gipson, 2004). The next layer of the tear film is an aqueous layer. The aqueous layer of the tear film is positioned between the mucin and lipid layers. The aqueous layer is mainly formed by the secretion of the lacrimal gland.

The aqueous layer is composed of various electrolytes, proteins, peptides, hormones, etc. Up to 150 different extracellular proteins and peptides have been detected in the tear film. In addition, proteins from degraded cells have also been detected. Lactoferrin, Tear lipocalin, and Lysozyme composed up to 90% of protein content. The total protein concentration in the tear film is about 5-6 mg/ml. The aqueous layer contains water-soluble mucins, such as MUC 5 and MUC 7, produced from conjunctival goblet cells (Hodges et al., 2013). Lactoferrin and Lysozyme are the major sources of antimicrobial activity in the tears (McDermott et al., 2011). The ability to bind free iron confers antimicrobial function to Lactoferrin. Removal of free iron from the media diminishes the availability of iron necessary for microbial growth. Lysozyme uses a different way to provide antimicrobial activity to tears. Lysozyme has a high capacity to attack the bacterial cell wall that provides antimicrobial activity (Flanagan et al., 2009; Gasymov et al., 1999). Tear lipocalin (TL), which comprises about 33% of total proteins is a major lipid-binding protein in tears. TL binds to a variety of lipids, such as fatty acids of different hydrocarbon chain lengths, phospholipids, glycolipids, cholesterol, etc. (Glasgow et al., 1995; Fullard et al., 1991). The promiscuous binding of tear lipocalin is well explained by the three-dimensional solution structure of TL determined by *Site-Directed Tryptophan Fluorescence* (Gasymov et al., 2001). It has been shown that the smaller-sized hydrophobic side chains positioned in the hydrophobic binding site of TL are the main determinant for promiscuous binding. TL shows multifunctional properties, among which are antimicrobial activity, cysteine proteinase inhibition, endonuclease activity, and retinol transport in tears (Yusifov et al., 2008; Gasymov et al., 2002).

The outermost layer of the tear film is the lipid layer secreted by the meibomian glands of the eyelids. The major function of the lipid layer is believed to prevent evaporation of the aqueous layer. The excessive evaporation observed in

some meibomian gland disorders results in corneal drying. This condition leads to epithelial erosions. It has been shown that the interaction of TL with the lipid layer stabilizes this layer to prevent its disruption. This results in an increased tear break-up time which is one of the stability parameters for the tear film.

Each layer of the tear film plays an important role to keep the cornea healthy and malfunction of any component may result in dry eye conditions. If not treated on time, dry eye conditions may result in blindness. Below we will provide a brief discussion of how the failure of any of these components leads to dry eye conditions in different ways. The membrane-associated mucin plays a pivotal role in keeping the cornea wet and tear film stable over the cornea. It has been shown that the ectodomain of the mucins acts as a barrier function to prevent bacterial adhesion. This domain also keeps the surface of the cornea wet. Enzymatic ectodomain shedding of membrane mucins at a normal rate is important for many biological functions. However, in some disorders, enhanced ectodomain shedding resulting from hyper enzyme activity creates naked epithelial cells that are prone to lipid contamination (Fig. 1).

Tear Lipocalin is the principal lipid-scavenging protein in human tears.

In normal conditions, TL is acting as a scavenger of the lipid from the epithelial cell surface (Glasgow et al., 1999; Gasymov et al., 2005). However, TL does not have enough capacity to remove lipids from the contaminated epithelial surface in excessive lipid binding events. As it is clear from this discussion, TL is a very important protein to keep the epithelial cells clean from lipids and prevent cornea surface drying. The experiments performed on the human cornea identify TL as a lipid scavenger from the cornea surface (Fig. 4). The cornea contaminated with the fluorescent phospholipids is seen as a dotted fluorescence surface under a fluorescent microscope. Incubation of the cornea with tears for 90 minutes almost fully removes the phospholipids from the cornea surface. However, removal is not evident when the contaminated cornea was incubated with the reconstituted tears where TL is removed. This experiment indicates that among many proteins, TL is the principal protein to keep the cornea surface free from lipids.

TL concentration was significantly lower in some dry eye patients indicating its importance for cornea health. Dry eye conditions may have resulted from meibomian dysfunction, even from the absence of pivotal lipids like phospholipids. The stability of the lipid layer is also provided by the interaction of TL with the lipid layer. Thus, proper functioning of all three layers is important to keep the cornea in a healthy condition.

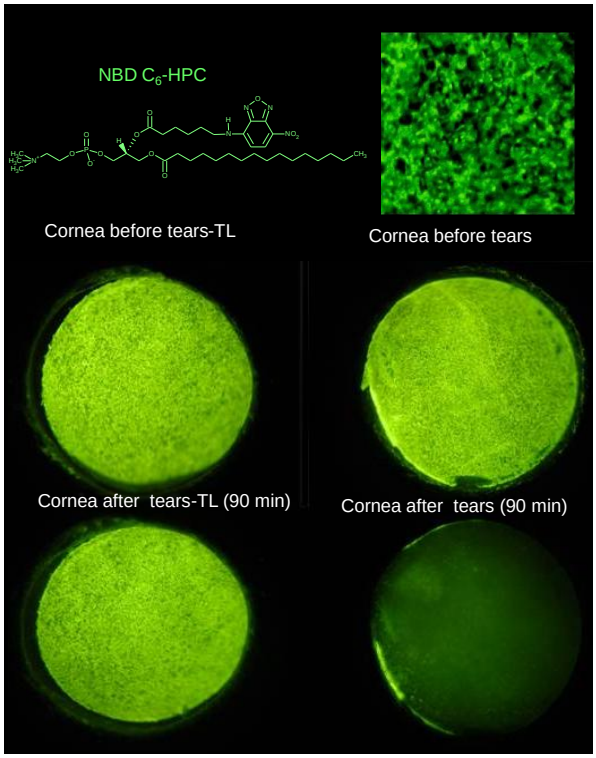

Fig. 4. The figure was modified from the work published in O.K.Gasymov et al., Tear Lipocalin: Evidence for a scavenging function to remove lipids from the human corneal surface, Investig. Ophthalmol. Vis, Sci., 2005, 46, 3589-3596.

One can get dry eye syndrome for various reasons that we have tried to describe above. Artificial tears of different origins are the main treatment options for dry eye diseases. Currently, there are no single best artificial tears that are suitable for all patients with dry eye syndromes. Artificial tears formulated with various polymeric materials, such as polyethylene glycol, carboxymethylcellulose/carmellose sodium, hydroxypropyl methylcellulose, etc have recently been critically reviewed (Semp et al., 2023).

Artificial tears with high concentrations of liposomes have been shown to be very effective to treat patients with dry eye disease with evaporative nature.

Effective artificial tears have also been formulated with protein components. Serum eye drops are an effective treatment for dry eye patients. The major protein component of the blood serum is albumin, which is a fatty acid-binding protein (Oktiadewiand Putra, 2023). It is possible that albumin as tear lipocalin, which is the major fatty acid binding protein in tears, may have properties of lipid scavenging from the corneal surface. On the other hand, albumin has high surface activity and may stabilize the superficial layer of the tears.

CONCLUSION

It should be noted that proper blinking is very important to keep the cornea lubricated. It is essential for contact lens wears. Today it is very difficult to imagine our life without computers. Spending much time in front of the computer, one should regularly exercise blinking, which is a treatment option for some people with dry eye syndrome. Various types of artificial tears are available to treat dry eye conditions. Finally, pharmaceutical industries have realized the importance of proteins to keep the cornea healthy. Artificial tears with essential tear proteins are now formulated and available in pharmacy stores. Although somewhat expensive; we believe that artificial tears with proteins should be the first choice for dry eye patients.

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O. Gasymov ORCID: https://orcid.org/0000-0001-7916-0354

A. Abdurahimov ORCID: https://orcid.org/ 0009-0004-8035-1018