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Review

Tear film lipid layer: A molecular level view☆

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ABSTRACT

Human cornea is covered by an aqueous tear film, and the outermost layer of the tear film is coated by lipids. This so-called tear film lipid layer (TFLL) reduces surface tension of the tear film and helps with the film re-spreading after blinks. Alterations of tear lipids composition and properties are related to dry eye syndrome. Therefore, unveiling structural and functional properties of TFLL is necessary for understanding tear film function under both normal and pathological conditions. Key properties of TFLL, such as resistance against high lateral pressures and ability to spread at the tear film surface, are directly related to the chemical identity of TFLL lipids. Hence, a molecular-level description is required to get better insight into TFLL properties. Molecular dynamics simulations are particularly well suited for this task and they were recently used for investigating TFLL. The present review discusses molecular level organization and properties of TFLL as seen by these simulation studies. This article is part of a Special Issue entitled: Biosimulations edited by Ilpo Vattulainen and Tomasz Róg.

Contents

1. Introduction

The human eye is a fragile organ directly exposed to the environment. It is particularly vulnerable to multiple external risk factors such as variations of temperature and humidity [1,2], air pollutions [3], and infectious microorganisms and viruses [4]. The tear film is a liquid layer covering the cornea and acting as a barrier between the eye and environment. The outermost layer of the tear film is composed predominantly of lipids and is referred to as the Tear Film Lipid Layer (TFLL). Its main role is to reduce surface tension of the tear film. Moreover, it helps with the tear film re-spreading after blinks, provides a smooth optical surface, and prevents water evaporation; although this last point is being recently disputed [5–7]. By reducing tear film surface tension and assisting in film re-spreading, TFLL is a key component for maintaining film stability.

The role of TFLL in tear film stabilization is of practical importance because alterations of lipid layer composition, distribution and thickness are associated with dry eye syndrome (DES) [8,9]. This eye alignment is related to fast breaking of the tear film and the enhanced exposure of corneal epithelium to air [10]. Therefore, understanding of TFLL properties is relevant for diagnosis and treatment of DES. Dry eye

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is one of the commonly reported eye conditions [11,12], highly prevalent in contact lens wearers [13,14] and is the main eye disorder in elderly population [15].

TFLL has been studied employing numerous experimental techniques ranging from direct optical microscopic observations of the film at human eye, through Langmuir balance measurements of tear extracts, to atomic force microscopy of model lipid mixtures mimicking TFLL composition. In those studies, tear film composition, structure, stability and dynamics were of main interest. Nevertheless, for a full understanding of fundamental properties of the tear film, a molecular-level insight is required. More specifically, one has to link macroscopic properties of the TLFF important for its function in the eye with TFLL properties at the nanometer level arising from interactions between individual chemical molecules constituting the film. While this task cannot be directly addressed by experimental techniques, it can be tackled by employing molecular dynamics (MD) simulation method.

In this review, we discuss recent studies in which MD simulations have been used to elucidate TFLL properties at the molecular level. We precede the discussion of these computational contributions by a brief description of the tear film and its lipid layer as well as by presentation of recent experimental studies of TFLL pertinent to molecular simulations.

2. Human tear film

The tear film is an aqueous phase covering the ocular surface. It is not a homogenous structure and it is classically divided into three relatively easy to distinguished layers [16,17] (see Fig. 1). Firstly, a mucin layer, 2.5 to 5 μm thick, which resides directly at the surface of cornea. It is composed predominantly of sugar-rich glycosylated proteins produced by epithelial cells and anchored to epithelium. The mucins form a gel-like structure providing an easily wettable surface and thus assisting in water re-spreading after blinks. Secondly, an aqueous layer, approximately 4 μm thick [18]. This is not a purely aqueous phase as it contains numerous water soluble and insoluble components such as electrolytes, proteins, peptides and small molecule metabolites [19]. Detailed proteomic studies of the tear film conclude that the most abundant proteins are tear lipocalin (~2 mg/ml) [20] and lysozyme (~2.5 mg/l) [21]. Lipocalin molecules are amphiphilic and surface active, therefore they are suggested to assist in tear film spreading [22]. The abundance of lysozyme is justified by its high antimicrobial activity [23]. The aqueous layer contains also soluble mucins which help during film re-spreading. While the main function of the aqueous phase is to present an optically smooth surface for light refraction, it also provides lubrication during blinks and eye movements, prevention of eye surface dehydration, protection against pathogens and small particles from air, and nutrition of corneal cells [19]. The fluid of the aqueous phase is secreted continuously by lacrimal glands with the rate of ~1.2 μl/minute [24]. The tears flow across the eye surface and are then removed via nasolacrimal duct. Such a constant flow allows for elimination of dirt particles and pathogens. The third, very outermost part of the tear film, dividing it from the external environment is a relatively thin, 0.015 to 0.160 μm thick [25], layer of lipids — TFLL. Many aspects regarding composition, structure and function of TFLL are still debated and these issues will be covered in the following chapter. Overall, the tear film composed of the three sublayers has a small thickness to area ratio ($\sim 10^{-3}$) displaying many properties characteristic to thin film systems [26].

Tear film is not a static system because of three key processes: tear flow, evaporation and blinking. While the dynamics associated with tear flow and evaporation can lead to a stationary process, the blinking is a source of significant non-regular disturbances of the tear film. The time of eyelid down- and up-movement in a spontaneous blink is approximately 100 ms and 250 ms, respectively [27]. Assuming a human eye diameter of 25 mm, average rate of the tear film compression and decompression is approximately 0.1 m/s and 0.04 m/s, respectively. Note that these values equal to 10 nm/μs and 4 nm/μs which, as will be discussed later, is comparable with compression and decompression rates in MD simulations. After each blink, the tear film must be at least partially re-spread at the surface of cornea. This process is characterized by a complex and not fully understood dynamics. Such factors as osmolality, gravitational forces, and evaporation were demonstrated to play a significant role during tear film spreading and the methods of fluid dynamics are typically applied for description of these phenomena (see the recent review by Braun [28]). Following each blink, the tear film moves upward over the corneal surface with a decaying velocity, and stabilizes after approximately 1 s [29]. Regarding lipids, their movement and TFLL reconstruction is relatively fast and is assumed to be driven by Marangoni effect due to a concentration gradient of polar lipids [28]. After some period of time, so-called tear film break-up time (TBUT), the film deteriorates, thins, and brakes. TBUT in humans

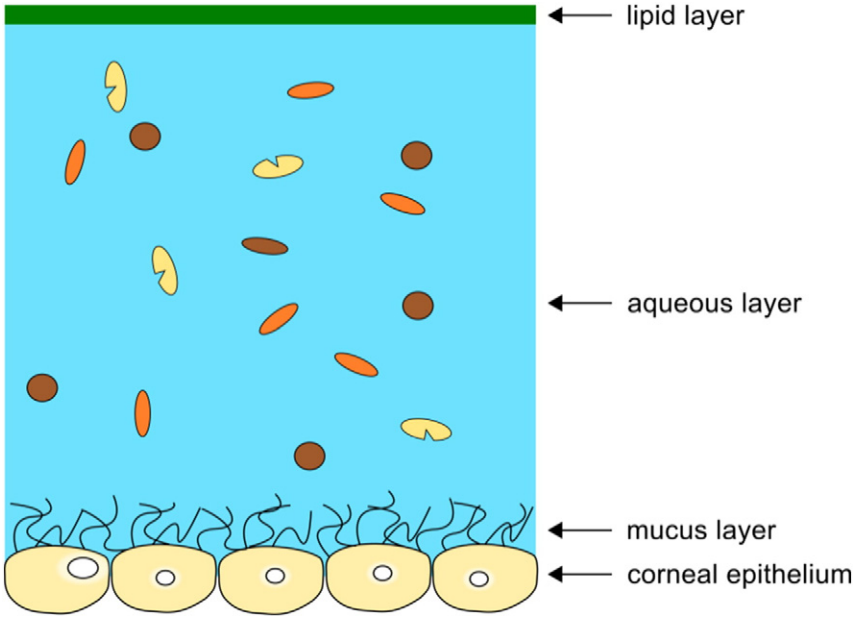

Fig. 1. Scheme of the tear film structure.