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Review article

Non-invasive objective and contemporary methods for measuring ocular surface inflammation in soft contact lens wearers – A review

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ABSTRACT

Contact lens wear is one of the primary risk factors for the development of ocular surface inflammatory events. The purpose of this review is to examine and summarize existing knowledge on the mechanisms of contact lens related ocular surface inflammation and the evidence for the effectiveness of current objective methods to measure ocular surface inflammation. Contact lens wear is postulated to trigger an inflammatory response on the ocular surface due to mechanical, chemical, hypoxic stress, or by the introduction of microbes and their toxins. Apart from the traditional signs of inflammation, such as swelling, oedema, redness and heat, on the ocular surface, other methods to measure ocular surface inflammation in sub-clinical levels include tear inflammatory mediator concentrations, conjunctival cell morphology, and corneal epithelial dendritic cell density and morphology. Tear inflammatory mediator concentrations are up- or down-regulated during contact lens wear, with or without the presence of associated inflammatory events. There is higher conjunctival cell metaplasia observed with contact lens wear, but changes in goblet cell density are inconclusive. Dendritic cell density is seen to increase soon after initiating soft contact lens wear. The long term effects of contact lens wear on dendritic cell migration in the cornea and conjunctiva, including the lid wiper area, require further investigation. Currently patient factors, such as age, smoking, systemic diseases and genetic profile are being studied. A better understanding of these mechanisms may facilitate the development of new management options and strategies to minimize ocular surface inflammation related to contact lens wear.

1. Introduction

The use of contact lenses is one of the primary risk factors associated with corneal and ocular surface inflammatory events [1–4]. It has been reported that soft contact lens related corneal inflammatory and infiltrative events occur in 7–44% of wearers per year and are associated with significant morbidity and economic cost (> $175 million US dollars in 2010, USA) [1,5–7]. Contact lens induced adverse events can be inflammatory and/or infectious in nature [2,8]. Contact lens wear can induce hypoxic or mechanical stress on the ocular surface and may also act as a vehicle for microbial inoculation, leading to pathogenic events ranging from subtle epithelial injury and infiltration by pathogens, antigens and white blood cells to the most severe microbial keratitis (MK)[9].

It has been hypothesized that a contact lens on the eye induces an ocular surface inflammatory process. Efron has comprehensively shown how contact lens wear can lead to the five cardinal signs of inflammation (mild and severe) that are clinically seen on the ocular surface namely- rubor (redness), calor (heat), tumor (swelling), loss of function (Functio laesa) and dolor (pain), which is encompassed as discomfort [10], and this is consistent with the Merriam- Webster dictionary definition of inflammation. Even though the forms of inflammations are mild in successful contact lens wearers, cardinal signs, such as hyperaemia [11], increased ocular temperature when wearing contact lens [12,13], symptoms [14], and corneal oedema in subjects who wear low oxygen transmissibility contact lenses [15], can be more readily observed than in non-contact lens wearers. These milder forms of inflammation can be managed by altering the contact lens material, fitting, decreasing wearing time and instillation of artificial tears [13,15–17]. However, in severe cases, the contact lens induced inflammation can lead to adverse events that warrant discontinuation of lens wear [18].

A large proportion of soft contact lens wearers report ocular dryness and discomfort [19,20]. It has been stated that this, so-called, ectopic corneal pain could be due to subclinical inflammation with the presence of normal tear secretion and corneal sensitivity [21,22]. Contact lens

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wear has been shown to induce higher ocular temperature and conjunctival hyperemia, which supports the notion that soft contact lens wear induces ocular surface inflammation, along with other compromised ocular surface parameters, such as lower tear stability and higher ocular surface staining [13,23–25].

This manuscript aimed to review the findings of these non-invasive contemporary techniques for detecting inflammatory responses at the cellular and molecular levels, including a) Ocular inflammatory response related to contact lens wear in humans; b) Recent objective methods used to evaluate the inflammatory responses on the ocular surface; and c) Potential factors that may be related to the risk of ocular inflammatory events in contact lens wearers.

2. Ocular surface inflammation in contact lens wear

The proposed mechanism driving this contact lens related inflammatory response can be described in two main steps: First, the ocular surface releases pro-inflammatory molecules and proteins [2,26] in response to the presence of a contact lens. These proteins then modulate the ocular surface (*i.e,* migration of antigen presenting cells and changes in the morphology of conjunctival cells) and these changes further drive the inflammatory cascade, in a vicious cycle (Fig. 1) [27]. These inflammatory responses can be measured noninvasively as is discussed in this manuscript (Fig. 1).

When a pathogen or foreign body is presented to the ocular surface, the innate immune system is activated, which leads to the secretion of certain inflammatory proteins by natural killer cells (NK cells) which in turn, can damage the ocular surface [28]. One family of the innate immune response proteins, the toll-like receptors (TLRs), can be activated by pathogen associated molecular patterns (PAMPs) on pathogens and endogenous ligands of intracellular components of dead cells, such as small nuclear ribonucleoprotein particles (snRNPs) [29]. In contact lens wear, TLRs are likely to be modulated by microbes and their products on the contact lenses and/or the damaged epithelial cells caused by contact lens wear [30]. After the activation of TLRs, Interleukin-1R associated kinase (IRAK) is activated and leads to activation of the Nuclear Factor kappa light chain enhancer of activated B cells (NF-kβ) pathway on the ocular surface. This leads to expression of multiple cytokines and chemokines, including interleukin (IL)-1α, IL-1β, IL-6, IL-8, IL-23, IL-17A, interferon (IFN)-γ and tumor necrosis factor (TNF)-α. Even though the activation of TLRs has been identified in dry eye [31], corneal inflammation and infection in animal studies [32,33], an appropriate animal model to study the role that TLRs in contact lens wear induced inflammation is warranted.

Damaged cells of the ocular surface can also release cytokines and chemokines and transform immature antigen presenting cells (APCs), which are dendritic cells and macrophages, into mature APCs [34]. APCs play a vital role in the activation of the immune system and the communication between B and T cells [35–37]. In the presence of certain up-regulating inflammatory mediators (IL-1, IL-6, IL-8, TNF- α and IFN-ϒ), infiltrating T cells, macrophages and HLA class II molecules on APCs increase in the epithelium on the ocular surface [38,39], which may up-regulate neuropeptides as inflammatory mediators [40,41]. Increased expression of inflammatory mediators was shown to correlate negatively with goblet cell density of the conjunctiva [42]. The released cytokines and chemokines may also lead to apoptosis of the ocular surface cells (Fig. 1). However, these relationships have not been fully investigated in contact lens wearers.

2.1. Inflammatory mediators on the ocular surface

More than 1500 proteins have been identified on the ocular surface and tear film [43,44]. Among them, at least 25 inflammatory mediators can be detected in tears in healthy subjects[45]. In this review, the known inflammatory mediators related to contact lens wear are briefly discussed in this section and the association with contact lens wear is

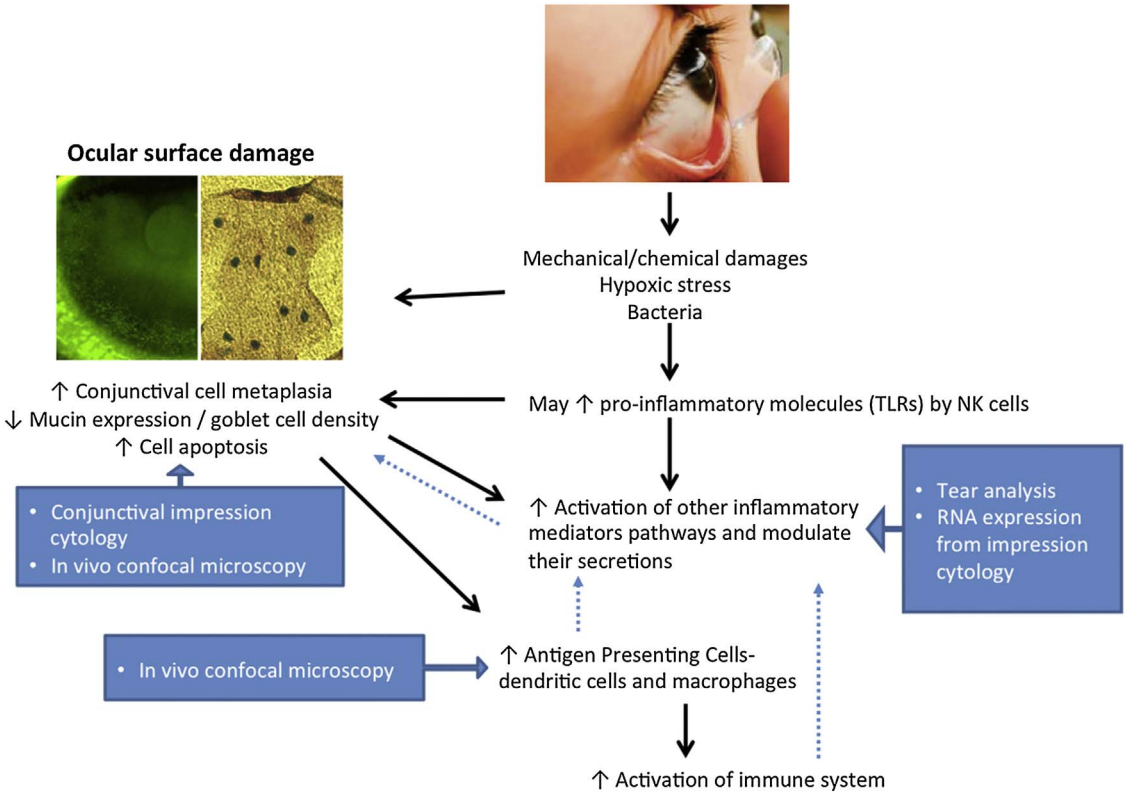

Fig. 1. Brief schematic diagram of ocular inflammation induced by contact lens wear and its measurements. TLRs: toll-like receptor; NK cells: natural killer cells. The blue boxes describe recent methods used to objectively measured lens induced inflammation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)