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Inflammation in Dry Eye Disease

How Do We Break the Cycle?

Michelle K. Rhee, MD,[2] Francis S. Mah, MD[1]

This article reviews the literature and summarizes the role of inflammation in dry eye disease. A PubMed search was performed using the keywords *inflammatory cycle and dry eye*. All searches were limited to articles published in or translated into the English language, dating from 1973 through March 2017. There were no restrictions on the study design. Advances in understanding the pathogenesis of dry eye disease has revealed that inflammation is a core driver: the so-called "vicious circle" of inflammation. Researchers continue to analyze the precise mechanisms by which inflammation occurs. This has led to therapeutic options to break the cycle. Continued animal and human studies reveal other potential sites for treatment in this complex host of disorders. *Ophthalmology 2017;124:S14-S19 © 2017 by the American Academy of Ophthalmology*

Establishment of Inflammation's Critical Role in Dry Eye Disease

Dry eye disease (DED) is a heterogeneous disorder of the ocular surface in which the common denominator is inflammation. The recognition of inflammation as a critical driver is reflected by its inclusion in the Dry Eye Workshop[1] definition of DED: "Dry eye disease is a multifactorial disorder of the tears and ocular surface, associated with symptoms of discomfort, visual disturbance, and tear film instability. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."

Researchers have been aware of the link between inflammation and DED for more than 40 years.[2–4] Histologic examination of lacrimal glands revealed lymphocytic infiltrates in patients with keratoconjunctivitis sicca without Sjögren's syndrome.[2] Another study challenged the concept that DED was caused by senile atrophy of the lacrimal gland, proposing that chronic inflammation was a contributor.[3] Stern et al[5] performed animal studies with systemic androgens or cyclosporine and concluded that cytokine- and receptor-mediated inflammation was universal to DED. Brignole et al[6] found that conjunctival cells from DED patients overexpressed inflammatory and apoptosis-related markers, and queried whether inflammation was a primary phenomenon or a result of DED. By 2001, inflammation was established as the common etiopathogenic mechanism in dry eye, with or without Sjögren's syndrome,[7] and both a cause and effect of DED.

Neuronal Feedback Loop

The lacrimal functional unit, defined as the ocular surface, lacrimal gland, and their neural interconnectivity, maintains ocular surface homeostasis, and disruption of this leads to tear film instability.[1,5] Tear production is regulated through a neural reflex loop; stimulation of nerves at the ocular surface or nasal mucosa sends impulses to the brain via the fifth cranial nerve, triggering a reflex response via nerves passing to the lacrimal glands. Pain, microbial or environmental insult, and emotion can stimulate this reflex loop. When any part of the lacrimal functional unit does not work properly, tear film instability and tear film hyperosmolarity occur. In earlier stages of the inflammatory cycle, ocular surface damage leads to a compensatory reflex stimulation of the lacrimal gland.[1] In experimental studies, excessive reflex stimulation of the lacrimal gland may induce a neurogenic inflammatory cytokine response within the gland, leading to the release of inflammatory markers into the tear film.[1,8]

Players in the "Vicious Circle" of Inflammation

The inflammatory cycle consists of afferent and efferent arms (Figs 1 and 2).[1,9,10,25] The afferent arm consists of stress to the ocular surface (environmental, endogenous, microbial, or a combination thereof, as well as hormone imbalance and genetic factors). When there is excess stress, production of cytokines, matrix metalloproteinases (MMPs), and chemokines ensues. This inflammatory setting prompts the maturation of antigen-presenting cells (APCs) and resident dendritic cells in the ocular tissue.[11,12] The specific initiating autoantigen has not been identified, but it is thought that the mature APCs bearing self-antigens travel to regional lymph nodes through the afferent lymphatic vessels, where they prime naïve T cells, which subsequently transform into the CD4+ T-helper cell subsets T_H1

Statement of Potential Conflict of Interest and Funding/Support: See page S19.

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Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ophtha.2017.08.029
ISSN 0161-6420/17

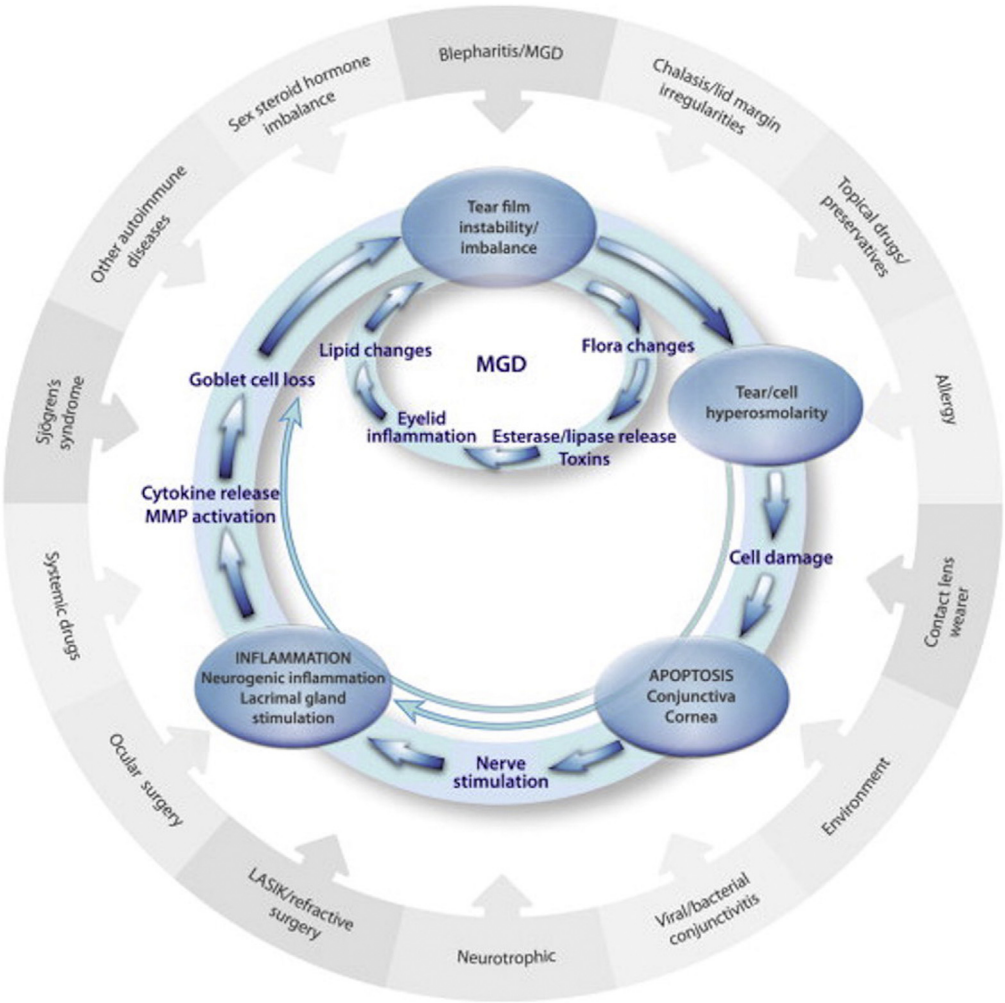

Figure 1. Diagram showing the vicious circle of dry eye disease.[9,10] MGD = meibomian gland dysfunction; MMP = matrix metalloproteinase. (Reprinted from Baudouin C. A new approach for better comprehension of diseases of the ocular surface. *J Fr Ophthalmol.* 2007;30(3):239–246; and Baudouin C, Aragona P, Messmer EM, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. *Ocul Surf.* 2013;11(4):246–258, with permission from Elsevier.)

and T_H17. These subsets are effector cells that migrate through the efferent vasculature to the ocular surface, where they are believed to induce epithelial damage via cytokine release.[11,12]

Tear film hyperosmolarity, tear film instability, and inflammation go hand in hand: tear film hyperosmolarity leads to ocular surface epithelial cell hyperosmolarity, which stimulates the inflammatory cascade involving mitogen-activated protein kinases and nuclear factor κ-light-chain-enhancer of activated B cells signaling pathways,[13,14] cytokines (interleukin [IL] 1α, IL-1β, tumor necrosis factor [TNF] α), and MMP-9.[15] T-cell recruitment and subsequent secretion of additional cytokines escalate the cycle of inflammation.[16] Specifically, CD4+ T cells are the primary infiltrating cells involved in DED.[12] The T-cell subsets T_H1 and T_H17 migrate to the ocular surface, where additional inflammatory mediators are released, including interferon γ, TNF-α, IL-2, and IL-17.[17,18] Interferon γ is linked to goblet cell dysfunction and death by altering mucin.[17] Murine experiments have shown T_H17 cells and their resultant IL-17 cytokines to be dominant players in the disruption of corneal barrier function.[18,19] Interleukin 17, along with IL-1 and TNF-α, seem to stimulate the release of MMPs by the corneal epithelium, which disrupt corneal epithelial tight junctions.[18] In addition, IL-17 upregulates expression of vascular endothelial growth factors C and D and promotes corneal lymphangiogenesis in DED. Newly formed lymphatic vessels provide a potential route by which APCs can travel from the ocular surface to these draining lymph nodes.[20] Interleukin 17 also has been reported to upregulate the expression of MMPs.[21,22]

Lam et al[23] analyzed the tears of dry eye patients and found that IL-6, IL-8, and TNF-α were significantly higher in DED with and without meibomian gland dysfunction (MGD) when compared with controls. They also found that the tear cytokine profiles were different in those with MGD; IL-12 was significantly higher in the dry eye group with MGD when compared with those without MGD. In addition, IL-6 and severity of irritation symptoms were significantly correlated, suggesting that IL-6 with mild dry eye may be the result of neuropathic ocular pain.

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