

Understanding the Science Behind the Inflammatory Cascade of Dry Eye Disease

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Dry eye disease (DED) affects tens of millions of patients everyday. Bench and clinical research, along with advancements in clinical diagnostic modalities have deepened our appreciation of the heterogeneity of DED and called attention to the inflammatory processes that occur in many patients. This article provides a concise review of the known afferent and efferent pathways of the ocular surface inflammatory response in dry eye disease. Understanding the pathophysiology behind DED will give clinicians a better understanding of this complex disease state and hopefully lead to earlier diagnosis of the condition and improved treatment modalities.

Keywords

Dry eye disease, ocular surface inflammation, pathophysiology, inflammatory cascade, afferent pathways, efferent pathways in ocular inflammation, hyperosmolar stress, tear film instability, adaptive immune response, conjunctival goblet cell dysfunction, ocular surface homeostasis

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Dry eye disease (DED) is the one of the leading causes of adult visits to ophthalmologists in the USA, with an estimated prevalence of 5–50% in adults over the age of 50 years.¹ Studies have estimated over 16 million patients have been diagnosed with DED, even in patients as young as 18–34.¹ As the “Baby Boom” population continues to age, the importance of identifying and diagnosing DED has become paramount. In 2017, the Tear Film & Ocular Society (TFOS) Dry Eye Workshop (DEWS) Definition and Classification Subcommittee released a revised definition of DED,² which acknowledges that ocular surface inflammation commonly plays an important role in the pathophysiology of the disease:

“Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.”

Bench and clinical research, along with advancements in clinical diagnostic modalities have deepened our appreciation of the heterogeneity of DED and called attention to the inflammatory processes that occur in many patients.² Ancillary testing to aid in the evaluation of inflammation in patients with DED may include conjunctival biopsy, impression cytology, and identification of inflammatory biomarkers such as MMP-9, human leukocyte antigen DR-1 (HLA-DR-1), and intercellular adhesion molecule 1 (ICAM-1) in tear and impression cytology samples. Understanding the normal anatomy of the ocular surface and the effects of the afferent and efferent pathways of DED will give clinicians a better understanding of the current rationale behind diagnostic methods and treatment options for this complex disease state.

Normal anatomy

The ocular surface is comprised of the cornea, conjunctiva, accessory lacrimal glands, and meibomian glands. The main lacrimal gland, the ocular surface, and their neural interconnections make up the lacrimal functional unit,³ and secrete fluids that create a complex tear film to help maintain ocular surface homeostasis. Anti-microbial molecules, immunoglobulins, immunomodulators, and mucins secreted by conjunctival goblet cells are all important tear film constituents which help regulate ocular immune homeostasis. Resident monocytes, macrophages, neutrophils, dendritic cells, Langerhans cells, natural killer cells, regulatory T cells, and effector T cells on the ocular surface also help mediate immune homeostasis. Disruption of any element of the lacrimal functional unit can lead to tear film instability, increased tear film osmolarity, and can trigger an inflammatory response on the ocular surface.

Afferent wing of the ocular surface inflammatory response in dry eye disease

A variety of extrinsic and intrinsic stressors may disrupt the lacrimal functional unit and lead to tear hyperosmolarity. Potential stressors include low humidity environments, topical medications, mechanical forces, desiccation, infection, aging, and dysfunctional tear secretion. Tear film instability

and hyperosmolarity can generate an innate immune response, which provides first-line non-specific defense and inflammatory reactions. The initiation of innate immune responses is mediated by pattern-recognition receptors, such as toll-like receptor 4, which has increased expression in murine models of induced DED.⁴ Receptor recognition triggers activation of inflammasomes, such as NLRP3 and NLRP6, which are activated in human corneal epithelial and murine models of DED, and subsequent secretion of proinflammatory cytokines such as interleukin-1 beta (IL-1β).⁵

In addition to generating an innate immune response, hyperosmolar stress generates a proinflammatory microenvironment on the ocular surface. *In vitro*, rat, and murine models have demonstrated that ocular surface hyperosmolar stress activates mitogen activated protein kinases,^{6,7} stimulates the expression of cytokines (IL-6, IL-8, IL-1α, IL-1β, TNF-α),⁶⁻⁹ and increases the production of matrix metalloproteinases (MMP-9, MMP-1, MMP-13, MMP-3).^{6,7,10} *In vitro* studies have also demonstrated that hyperosmolarity can induce apoptosis in cultured corneal epithelial cells,¹¹ and experimentally induced DED in murine models has also demonstrated apoptosis of ocular surface tissue cells.¹²

Hyperosmolar stress can trigger an adaptive immune response through overexpression of HLA-DR in the conjunctival epithelium¹³ and increased levels of chemokines such as CCL20, CXCL9, CXCL10, and CXCL11 in the tear film and ocular surface.^{14,15} These chemokines and receptors promote activation of antigen presenting cells, especially corneal dendritic cells,¹⁶ and recruitment of inflammatory mediators. Increased corneal lymphangiogenesis along with increased honing of antigen presenting cells (APCs) to draining lymph nodes have been observed in murine models of induced DED.¹⁷ Once they are in draining lymph nodes, APCs then prime naïve T cells, presumably to unknown ocular surface antigens.¹⁸ Primed effector Th1, Th17, and natural killer (NK) cells travel back to the ocular surface, where they secrete interferon-gamma (IFNγ) and IL-17.¹⁹⁻²²

Efferent wing of the ocular surface inflammatory response in dry eye disease

Secretion of IFNγ by Th1 and NK cells promotes loss of conjunctival goblet cells, which nurture the tear film through the provision of proteins and

mucin. In murine culture models, it has been observed that even low exposure to IFNγ results in structural changes in goblet cells and reduced proliferation.²³ In murine models, exogenous administration of IFNγ and induced DED result in decreased goblet cell density.^{24,25} Compared to healthy individuals, subjects with tear dysfunction have been observed to have increased expression of conjunctival IFNγ, with higher levels of IFNγ correlating with increased goblet cell loss.²⁶ In addition to promoting loss of conjunctival goblet cells, it has been demonstrated in murine models of Sjögren's Syndrome that IFNγ also has a role in inducing lacrimal acinar apoptosis through caspase induction.²⁷

While IFNγ has been implicated in conjunctival goblet cell and lacrimal acinar loss, IL-17 secreted by Th17 cells plays an important role in corneal barrier disruption and induction of matrix metalloproteinase production.²¹ Matrix metalloproteinases are enzymes involved in extracellular matrix degradation and, on the ocular surface epithelium, they promote barrier disruption by destroying tight junctions. Desiccating stress stimulates increased corneal epithelial levels of MMP-1, -3, -9, and -10 in murine models of DED.²⁸ MMP-9 has especially been implicated in the pathogenesis of DED as MMP-9 knockout mice are more resistant to corneal epithelial disruption than wildtype controls in models of induced DED.²⁹ Investigations using impression cytology have demonstrated that patients with dry eye have significantly higher levels of MMP-9 and IL-17 in the conjunctival epithelium compared to healthy controls.²¹ In murine models, desiccating stress leads to ocular surface infiltration by T cells and increased production of IL-17. Neutralization of IL-17 leads to reduced levels of MMP-9 and MMP-3 *in vitro*.²¹

Conclusion

Hyperosmolar stressors and tear film instability trigger the innate immune response and secretion of numerous cytokines to create a vicious cycle that perpetuates the signs and symptoms of DED. Understanding the afferent and efferent pathways of DED will give clinicians a better understanding of this complex disease state and hopefully lead to earlier diagnosis and improved treatment. Application of this greater comprehension of the mechanism of disease to clinical practice will hopefully lead to fewer patients suffering from undiagnosed DED. □

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