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The Pathophysiology of Dry Eye Disease

What We Know and Future Directions for Research

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Clinical and laboratory studies performed over the past few decades have discovered that dry eye is a chronic inflammatory disease that can be initiated by numerous extrinsic or intrinsic factors that promote an unstable and hyperosmolar tear film. These changes in tear composition, in some cases combined with systemic factors, lead to an inflammatory cycle that causes ocular surface epithelial disease and neural stimulation. Acute desiccation activates stress signaling pathways in the ocular surface epithelium and resident immune cells. This triggers production of innate inflammatory mediators that stimulate the production of matrix metalloprotease, inflammatory cell recruitment, and dendritic cell maturation. These mediators, combined with exposure of autoantigens, can lead to an adaptive T cell–mediated response. Cornea barrier disruption develops by protease-mediated lysis of epithelial tight junctions, leading to accelerated cell death; desquamation; an irregular, poorly lubricated cornea surface; and exposure and sensitization of epithelial nociceptors. Conjunctival goblet cell dysfunction and death are promoted by the T helper 1 cytokine interferon gamma. These epithelial changes further destabilize the tear film, amplify inflammation, and create a vicious cycle. Cyclosporine and lifitegrast, the 2 US Food and Drug Administration–approved therapies, inhibit T-cell activation and cytokine production. Although these therapies represent a major advance in dry eye therapy, they are not effective in improving discomfort and corneal epithelial disease in all patients. Preclinical studies have identified other potential therapeutic targets, biomarkers, and strategies to bolster endogenous immunoregulatory pathways. These discoveries will, it is hoped, lead to further advances in diagnostic classification and treatment. *Ophthalmology 2017;124:S4-S13 © 2017 by the American Academy of Ophthalmology.*

Dry Eye—A Multifactorial and Self-perpetuating Inflammatory Disease

Knowledge regarding the pathophysiology of dry eye has advanced tremendously over the past 2 decades and continues to evolve. Although tear disorders were traditionally classified by deficient component (e.g., aqueous or lipid), or as aqueous deficient or evaporative, the reality is that most patients experiencing symptoms or signs of tear dysfunction have multiple risk factors and disease or dysfunction of more than 1 tear-producing cells/glands that result in an unstable tear film.[1] Tear instability is accompanied by increased tear osmolarity (either in area of tear breakup or diffusely), which activates stress signaling pathways in the ocular surface epithelium and resident immune cells and triggers production of innate inflammatory molecules that initiate a vicious self-perpetuating cycle (Fig 1) that may lead to further decline in tear function and worse symptoms.[2,3] The numerous extrinsic (e.g., desiccating environment, exposure) and intrinsic (e.g., aging, autoimmunity, drying medications) factors that can contribute to this inflammatory cycle demonstrate why it is often difficult to ascribe a single cause for most cases of dry eye disease and the importance of addressing all modifiable risk factors.

The ocular surface is a very unique exposed mucosa. It is covered with a specialized stratified epithelium that serves as a barrier to environmental, microbial, and inflammatory insults. Next to the intestine, the conjunctival epithelium has the second-highest density of mucus-producing goblet cells. It also harbors a variety of resident immune cells, such as natural killer cells, dendritic cells, macrophages, and γδ, CD4, and $CD8^+$ T cells that function primarily in antimicrobial defense but may participate in the dry eye pathogenesis.[4–6] The cornea epithelium must withstand daily environmental challenges while maintaining clarity and comfort. The lacrimal glands and ocular surface epithelia produce an array of antimicrobial factors including, α and β defensins, IgA, lactoferrin, and lysozyme that are present in the tear film and function to maintain a paucibacterial microenvironment.[7–20] Many of the mechanisms to maintain ocular surface and glandular homeostasis are disrupted in dry eye (Fig 2). Studies performed in animal models and dry eye patients have found that desiccation is a potent stress (in the same magnitude to microbial products) to the ocular surface that initiates a secondary immune response that can lead to a vicious cycle (Fig 1).[21–27] Hyperosmolar stress has a direct proinflammatory effect on the ocular surface epithelium. It has been shown to activate mitogen-activated protein kinases (MAPKs); stimulate secretion of proinflammatory cytokines (e.g., interleukin [IL]-1β, TNF-α,

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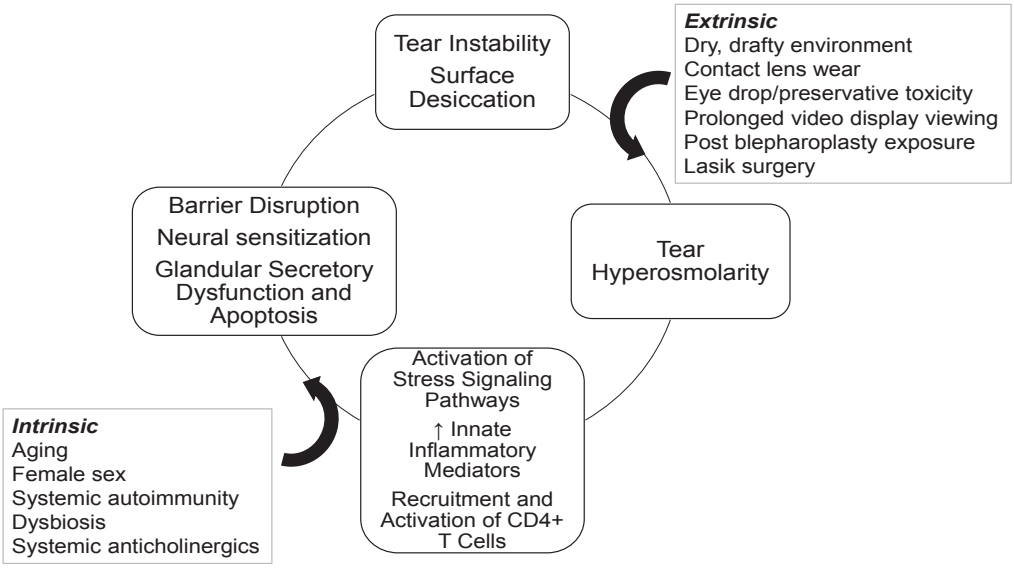

Figure 1. Dry eye inflammatory cycle that can be initiated or amplified by extrinsic and intrinsic factors that cause tear instability and tear composition changes, including hyperosmolarity, that activate stress signaling pathways in the ocular surface cells, which triggers production of innate inflammatory mediators, which can lead to recruitment and activation of CD4+ T cells, which produce cytokines that cause corneal, conjunctival, and lacrimal gland epithelial disease.

and IL-6), chemokines, and matrix metalloproteinases (MMP) such as MMP-3 and MMP-9; and induce apoptosis.[22,23,26,28–38] The interaction of these inflammatory mediators is complex and they have been shown to upregulate each other, thus amplifying the inflammatory cascade. For example, IL-1β stimulates the production of TNF-α and MMP-3, among other factors.[31,32,39,40] In turn, TNF-α stimulates MMP-9 and MMP-3, which is a physiological activator of MMP-9.[41,42] MMP-9 contributes to corneal barrier disruption by lysing tight junctions in the superficial epithelium.[23,26,43] MMP-9 knockout mice are resistant to corneal barrier disruption when exposed to desiccating stress, and MMP inhibitors, such as corticosteroids and doxycycline, have shown potential in preventing desiccation-induced corneal epithelial barrier disruption in animal models.[26,43–45] A point-of-care MMP-9 detection system (InflammaDry, RPS, Sarasota, FL) is approved for detecting elevated levels of MMP-9 in tears of dry eye patients.[46–50] Increased tear MMP-9 has also been detected in other ocular surface diseases, such as atopic and vernal keratoconjunctivitis, corneal ulceration, recurrent corneal erosions, and ocular burns, that also have corneal barrier disruption.[51–63] Detection of elevated tear MMP-9 provides a rationale for use of anti-inflammatory/protease therapies in these conditions.

Ocular surface epithelial cells also secrete chemokines that attract inflammatory cells. Increased levels of chemokines CCL20 (MIP3α), CXCL9 (MIG), CXCL10 (IP-10), and CXCL11 (I-TAC) and their receptors were noted in ocular surface cells and/or tears of dry eye patients and mice with experimentally induced dry eye.[64–68] Genetic deletion or pharmacologic blockage of certain chemokines or chemokine receptors (CCL20, CCR6, or CXCR3) prevented the development of desiccation-induced ocular surface disease and decreased pathogenicity of autoreactive T cells in mouse models of dry eye.[69,70]

Another effect of desiccation is upregulation of innate inflammatory pathways in the epithelium, including the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3), toll-like receptor, and oxidative stress pathways.[29,30,71–80] Antioxidants have shown therapeutic potential for treating dry eye in preclinical culture or mouse studies and in a pilot clinical trial.[30,34,81–85]

Metaplasia and goblet cell loss in the conjunctival epithelium is a well-recognized feature of aqueous tear deficiency.[86–92] The most severe ocular surface diseases, such as Stevens-Johnson syndrome, mucous membrane pemphigoid, graft-versus-host disease, and severe alkali burns involving the conjunctiva often have complete loss of conjunctival goblet cells.[93–96] T helper cytokines have been found to modulate conjunctival goblet cell differentiation. The Th2 cytokine IL-13 stimulates proliferation and mucus production, whereas the Th1 cytokine interferon gamma (IFN-γ) induces goblet cell entrapment, expression of cornified envelope precursors, decreased mucus production, unresponsiveness to cholinergic stimulation, endoplasmic reticulum (ER) stress, and unfolded protein response and apoptosis.[27,97–104] In addition to producing tear-stabilizing mucins,[105,106] goblet cells also produce immunoregulatory factors, such as TGF-β and retinoic acid.[104,107] Crosstalk between goblet cells and dendritic cells is critical to maintaining immune tolerance in mucosal tissues.[108] Goblet cell–associated passages that deliver surface antigens to the underlying dendritic cells and promote tolerance have been identified in both intestine and conjunctiva.[108,109] Mice with deletion of the SAM pointed domain containing ETS transcription factor gene (*Spdef* knockout) are devoid of goblet cells, develop

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