Dry eye disease (DED), also known as keratoconjunctivitis sicca, is a multifactorial disorder of the tears and ocular surface. Common symptoms of DED include dryness, irritation, foreign body sensation, light sensitivity, and itching. It is estimated that almost 5 million Americans 50 years and older have DED, and millions more experience episodic symptoms of dry eye; of these, approximately two-thirds are women. The prevalence of DED rises dramatically with increasing age, and as older populations grow, so too will the burden of DED-associated morbidity. Dry eye disease can hinder the performance of activities of daily living, and DED is associated with an overall decrease in quality of life. Patients with DED are significantly more likely than the general population to experience symptoms of anxiety and depression. Risk factors for the development of DED include advanced age, female sex, hormonal imbalance, autoimmune disease, abnormal corneal innervation, vitamin deficiency, environmental stress, contact lens use, infection, medication use, and ophthalmic surgery. The pathogenesis of DED is not fully understood; however, it is recognized that inflammation has a prominent role in the development and amplification of the signs and symptoms of DED.

The ocular surface system consists of the cornea, conjunctiva, lacrimal glands, meibomian glands, nasolacrimal duct, and their associated tear and connective tissue matrices, as well as the eyelids and eyelashes, all integrated by continuous epithelia and interconnected nervous, endocrine, immune, and vascular systems. Factors that disturb the delicate homeostatic balance of the ocular surface system can adversely affect tear film stability and osmolarity, resulting in osmotic, mechanical, and inflammatory damage. Exposure of ocular surface epithelial cells to elevated tear osmolarity activates stress-associated mitogen-activated protein kinases, such as c-Jun N-terminal kinase, extracellular signal-related kinase, and p38. Mitogen-activated protein kinase signaling path-
ways stimulate the transcription factors nuclear factor κB and activator protein 1, thereby initiating the production of proinflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs). These inflammatory mediators promote the activation (maturation) of immature antigen-presenting cells (APCs) and induce their migration to draining lymphoid tissues (Figure 1). The APCs are responsible for priming naïve T cells in the lymphoid compartment, leading to the expansion of autoreactive CD4+ helper T cell (T-H) subtype 1 and T-H17 cells that subsequently infiltrate the ocular surface, where they secrete additional proinflammatory cytokines. Helper T cell subtype 1-secreted interferon (INF)-γ upregulates the production of chemokines, chemokine receptors, and cell adhesion molecules (CAMs) that facilitate the ingress of pathogenic immune cells, including T-H17 cells that secrete interleukin (IL) 17, which further promotes epithelial damage by stimulating the production of proinflammatory cytokines and MMPs. Regardless of the origin, a self-perpetuating cycle of inflammation develops that is central to the pathogenesis of DED.

**EPITHELIOPATHY**

Epitheliopathy is one of the most easily recognizable clinical features of DED. Staining the ocular surface with diagnostic dyes, such as fluorescein, rose bengal, and lissamine green, provides a practical method for evaluating ocular surface integrity. Dry eye disease increases epithelial cell density and thickness, decreases epithelial cell size, and increases epithelial cell turnover. Inflammation of the ocular surface is intimately linked to this epithelial dysfunction. The proinflammatory cytokines IL-1 and INF-γ cause squamous metaplasia of ocular surface epithelial cells, and INF-γ decreases goblet cell differentiation. Apoptosis of ocular surface cells in DED can be induced by intrinsic (stress-associated mitogen-activated protein kinase) and extrinsic (tumor necrosis...
factor [TNF] and Fas/Fas ligand) pathways.\textsuperscript{19,20} The MMPs (eg, MMP-9) are produced in response to desiccating stress and promote corneal extracellular matrix degradation and epithelial cell loss.\textsuperscript{21} Helper T cell subtype 17–secreted IL-17 was recently shown to disrupt corneal epithelial barrier function.\textsuperscript{14}

LYMPHANGIOGENESIS

Traditionally, angiogenesis has been thought to involve lymphangiogenesis and hemangiogenesis, producing different lymphatic vessels and blood vessels, respectively. Dry eye disease involves a unique form of pathologic angiogenesis that produces lymphangiogenesis without associated hemangiogenesis, and this is observed in experimental and clinical settings. The presence of lymphatic endothelial marker 1–staining monocytic cells in the conjunctiva has been described and linked to the growth of lymphatic vessels into the cornea.\textsuperscript{22} Immunohistochemical analysis of dry eye corneas identified the infiltration of lymphatic endothelial marker 1–expressing macrophages and lymphatic vessels (Figure 2).\textsuperscript{23} Dry eye induction increases the expression of factors that promote lymphangiogenesis, including vascular endothelial growth factor (VEGF) C and VEGF-D and associated receptors VEGFR-2 and VEGFR-3. Vascular endothelial growth factor A is also upregulated, contributing to lymphangiogenesis through the recruitment of VEGF-C– and VEGF-D–producing macrophages. In addition, recent data suggest that Th17-secreted IL-17 upregulates expression of VEGF-C and VEGF-D and promotes corneal lymphangiogenesis in DED.\textsuperscript{24} Pathogenic immune cells are present in the regional lymph nodes of DED-induced mice.\textsuperscript{13} The identification of newly formed lymphatic vessels in the cornea provides a potential route by which antigens and APCs can travel from the ocular surface to these draining lymph nodes. Accordingly, blockage of lymphangiogenesis may prove to be an effective treatment for DED.\textsuperscript{25}

NEUROPATHY

The corneal epithelium has approximately 7000 nerve endings per square millimeter, making the cornea one of the most densely innervated tissues in the human body.\textsuperscript{26} The nervous system is an important component of the ocular surface system, and optimal functioning of the corneal nerves is essential for the maintenance of a healthy ocular surface. In healthy corneas, nerve endings are located between epithelial wing cell layers, where they are protected from external stimuli.\textsuperscript{27} Decreased density and altered morphologic structure of the subbasal nerves have been reported in DED-induced corneas.\textsuperscript{28-33} These abnormalities are generally found to correlate with DED severity. Elevated tear osmolarity induces inflammatory-mediated epitheliopathy that results in the exposure of corneal nerves to mechanical and inflamm-
tory insults. Inflammatory cytokines in turn increase the synthesis of neurotrophic factors that stimulate nerve growth, potentially explaining the altered nerve morphologic structure (nerve sprouts, tortuosity, and thinning) commonly observed in DED. Corneal nerve abnormalities lead to further ocular surface damage and help perpetuate the vicious inflammatory cycle of DED.

Molecular MEDIATORS

Cytokines

Cytokines are signaling molecules that mediate intercellular communication. The production of proinflammatory cytokines is upregulated by osmotic, inflammatory, and mechanical damage. The term interleukin alludes to intercellular communication between leukocytes; however, many different cell types are capable of producing and responding to cytokines. For example, virtually all nucleated cells, including epithelial cells of the ocular surface, are capable of producing IL-1, IL-6, and TNF. Clinical studies consistently report elevated levels of these cytokines in the tears of patients with DED. Similar trends are noted in the conjunctival epithelium, which contains elevated levels of IL-1, IL-6, TNF, and transforming growth factor β1. Several additional cytokines have been isolated from the ocular surface of patients with DED, including IL-2, IL-4, IL-5, IL-10, and IFN-γ. These clinical findings have been corroborated by studies involving experimental models of DED (Figure 3).

Chemokines

Chemokines are cytokines that regulate the chemotaxis, or directed migration, of immune cells. The chemokine IL-8 (CXCL8) is consistently identified in the tears and conjunctiva of patients with DED. Interleukin 8 can be produced by any cell with a toll-like receptor (eg, epithelial cells and macrophages), and it is a neutrophil chemoattractant involved in the innate immune response. The closely related chemokines CXCL9, CXCL10, and CXCL11 are elevated in the tear film and ocular surface of patients with DED. These latter chemokines are produced in response to IFN-γ and function as T-cell chemoattractants on binding to the chemokine (CXCR3 motif) receptor. Animal models of DED provide further evidence of chemokine activity. The chemokine (CC motif) ligands CCL3 (macrophage inflammatory protein 1α) and CCL4 (macrophage inflammatory protein 1β) are upregulated in DED. These chemokines are produced by macrophages, recruit inflammatory cells (such as neutrophils), and upregulate the production of proinflammatory cytokines. Another potent T-cell chemoattractant, CCL5 (RANTES), is upregulated in DED. The chemokine receptors CCR1, CCR2, CCR5, and CXCR3 have been implicated in the pathogenesis of DED and represent promising targets for immunomodulation.

Matrix Metalloproteinases

Matrix metalloproteinases are endopeptidases involved in tissue remodeling. Corneal epithelial cells produce MMP-1, MMP-3, MMP-9, and MMP-13 in response to hyperosmolar stress. Experimental dry eye increases MMP-1, MMP-3, MMP-9, and MMP-10 levels in the tears and corneal epithelium of mice. Elevated levels of pro–MMP-9 and increased activity of MMP-9 have been identified in the tears of patients with dry eye. Knockout of MMP-9 tempers the severity of experimental dry eye, implicating MMP-9 in the pathogenesis of DED. Not only is MMP-9 produced by granulocytes, but it is also involved in the activation of latent CL-8β. The MMPs are thought to modulate the severity of DED by promoting corneal extracellular matrix degradation and epithelial cell loss. Doxycycline, a tetracycline derivative, ameliorates DED by inhibiting the activity of MMPs, primarily MMP-9, promoting ocular surface integrity.

Major Histocompatibility Complex Class II and Costimulatory Molecules

The expression of various cell-associated immunomodulatory molecules is increased in DED. The ocular surface of patients with dry eye contains elevated levels of HLA type DR (HLADR), CD40, CD154 (CD40L), CD80, CD86, Fas, and Fas ligand. HLADR is a major histocompatibility complex (MHC) class II cell surface receptor involved in antigen presentation. CD40, CD154, CD80, and CD86 are costimulatory molecules involved in APC–T-cell interactions. Increased expression of these molecules suggests that antigen (presumably autoantigen) presentation occurs efficiently in DED. Fas is a death receptor that induces apoptosis on binding to Fas ligand. The presence of these molecules in the conjunctiva and lacrimal glands of patients with dry eye is indicative of cellular infiltration, as these molecules are responsible for regulating the activity of immune cells.
Cell adhesion molecules are cell surface proteins that facilitate cellular migration by binding to extracellular matrix components. Cell adhesion molecules promote the infiltration of immune cells into the ocular surface of patients with dry eye. Elevated levels of intercellular adhesion molecule 1 and vascular CAM-1 have been identified in the conjunctiva and lacrimal glands of patients with dry eye.\textsuperscript{40-68} Intercellular adhesion molecule 1 binds to lymphocyte function–associated antigen 1. Vascular CAM-1 is expressed by the vascular endothelium and binds to immune cell–expressed very late antigen 4, also known as integrin α4β1. Treatment with monoclonal antibodies against murine intercellular adhesion molecule 1 and lymphocyte function–associated antigen 1 resulted in decreased ocular surface inflammatory infiltrates in experimental DED.\textsuperscript{66} Topical inhibition of very late antigen 4 decreases dry eye severity and suppresses inflammation in a murine model of DED.\textsuperscript{40}

CELLULAR MEDIATORS

Antigen-Presenting Cells

Antigen-presenting cells are sentinel cells of the immune system that respond to danger signals (eg, microbial pathogens) by internalizing, processing, and presenting antigens.\textsuperscript{70} The phenotype, or state of maturation, of an APC determines its function. Immature APCs express low levels of MHC class II and costimulatory molecules (eg, CD80 [B7.1]); although immature APCs are proficient at capturing antigens, they are inefficient at presenting antigens and promoting T-cell activation. Inflammatory microenvironments can induce APC maturation via increased expression of MHC class II and costimulatory molecules, rendering APCs efficient at priming T cells.\textsuperscript{71} Antigen-presenting cells of the ocular surface include monocytes and macrophages, dendritic cells (DCs), and Langerhans cells (LCs). The LCs are the only cells in the corneal epithelium that constitutively express MHC class II.\textsuperscript{72} The peripheral corneal epithelium contains MHC class II–positive and MHC class II–negative LCs, while the central cornea contains only MHC class II–negative, costimulatory molecule–negative LCs; however, LCs of the central cornea are capable of expressing MHC class II and costimulatory molecules following inflammatory stimuli.\textsuperscript{73} The anterior corneal stroma contains differentiated and undifferentiated resident monocytic cell–derived DCs.\textsuperscript{73,74} Recently, the presence of a unique population of (non-LC) langerin–positive DCs was reported in the corneal stroma.\textsuperscript{73} In contrast, MHC class II–positive DCs are abundantly present in the conjunctiva. In vivo microscopy reveals that DED dramatically increases the presence of DCs in the central corneal epithelium of patients.\textsuperscript{75} Similarly, in DED–induced murine corneas, there is evidence of an influx of CD11b\textsuperscript{+} APCs (Figure 4). The APC–mediated priming of T\textsubscript{H}1 and T\textsubscript{H}17 cells against autoantigens has been proposed as a potential source of autoimmunity in DED.\textsuperscript{77}

**Figure 4.** Treatment with monoclonal antibodies against murine intercellular adhesion molecule 1 and lymphocyte function–associated antigen 1 resulted in decreased ocular surface inflammatory infiltrates in experimental DED.\textsuperscript{66} Topical inhibition of very late antigen 4 decreases dry eye severity and suppresses inflammation in a murine model of DED.\textsuperscript{40}

**Adhesion Molecules**

**Cellular Mediators**

**Antigen-Presenting Cells**

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**Effector T Cells**

T-cell infiltration of the ocular surface is a pervasive finding in DED (Figure 5). CD4\textsuperscript{+} T cells, including IFN-γ–secreting T\textsubscript{H}1 cells and IL-17–secreting T\textsubscript{H}17 cells, are thought to be the primary effector T cells of DED.\textsuperscript{13,14} Although the relative contributions of T\textsubscript{H}1 and T\textsubscript{H}17 cells remain unclear, recent findings suggest that T\textsubscript{H}17 cells have a prominent role in the pathogenesis of DED.\textsuperscript{14,77-79} This is an important finding, particularly given that T\textsubscript{H}1 and T\textsubscript{H}17 cells differentiate via divergent pathways. Elevated expression of IL-6 has long been recognized in DED; however, the role of IL-6 in the pathogenesis of DED has been largely unknown. It is understood that IL-6 and transforming growth factor β promote the differentiation of T\textsubscript{H}17 cells, while transforming growth factor β suppresses T\textsubscript{H}1–mediated responses. The attenuating effects of CD4\textsuperscript{+}CD25\textsuperscript{+}Foxp3\textsuperscript{+} regulatory T cells (Tregs) have been described in models of ocular surface inflammation, but the inability of Tregs to suppress DED has been incompletely explained. It was recently demonstrated that the T\textsubscript{H}17, but not T\textsubscript{H}1, cell subset is resistant and functionally antagonistic to Treg–mediated suppression in DED, and in vivo blockade of IL-17 significantly decreases DED severity.\textsuperscript{78}

**Regulatory T Cells**

Regulatory T cells are a distinct family of T cells involved in the suppression of immune responses. Treg abnormalities in systemic autoimmune diseases associated with DED, such as Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis, have long been recognized.\textsuperscript{80} Treg abnormalities were recently implicated in the development of experimental DED. Nude mice that lack CD4\textsuperscript{+}CD25\textsuperscript{+}Foxp3\textsuperscript{+} Tregs were adoptively transferred with DED–primed T cells and subsequently developed Sjögren syndrome–like DED.\textsuperscript{81} Tregs have been shown to suppress DED–associated ocular surface inflammation.\textsuperscript{82} The resistance of effector T cells, particularly T\textsubscript{H}17 cells, to Treg–mediated suppression has been identified as an important factor in the pathogenesis of DED.\textsuperscript{78}

**Natural Killer Cells**

Natural killer (NK) cells are large granular lymphocytes capable of secreting proinflammatory cytokines and killing infected or transformed cells. Although NK cells, T cells, and B cells are derived from common bone marrow–derived lymphoid progenitors, they differ significantly in phenotype and function. Natural killer cells have been implicated in the pathogenesis of various autoimmune diseases; however, little is known about the function of NK cells in DED. Investigations of NK cell activity and frequency in Sjögren syndrome have yielded varying results.\textsuperscript{83,84} Natural killer cells do not seem to infiltrate the conjunctival epithelium of patients with dry eye.\textsuperscript{85} However, IFN-γ–secreting NK cells located in draining lymph nodes have been implicated in the early development of experimental DED.\textsuperscript{86}
Numerous tests and guidelines are available to help direct the clinical management of DED. Unfortunately, decision making is often complicated by a lack of concordance among the signs and symptoms of DED. Some of the techniques being used to investigate inflammation and dry eye in the experimental setting may one day be available in the clinical setting to help overcome this incongruity. As previously described, many markers of inflammation can be identified in the tears and conjunctiva of patients with DED. Some of these markers, including IL-6 and HLADR, correlate with clinical measures of disease severity and treatment efficacy. In vivo confocal microscopy is being used to examine the effects of ocular surface inflammation on immune cell infiltration and on morphologic structure of epithelial cells, subbasal nerves, and meibomian glands. As experimental techniques that evaluate ocular surface inflammation are further refined, they may become valuable tools in the physician’s options. Diagnostic methods that combine conventional tests with experimental measures of inflammation (eg, the scraping cytology score system) have been proposed, potentially bridging the gap between bench and bedside.

ANTI-INFLAMMATORY TREATMENT

Cyclosporine A

Cyclosporine A exerts immunosuppressive activity through several pathways. It forms a complex with cyclophilin that inhibits the calcineurin phosphatase pathway responsible for the transcription of T-cell-activating cytokines (such as IL-2). Cyclosporine A binds cyclophilin D, inhibiting the activity of the mitochondrial permeability transition pore and subsequent cytochrome c–mediated apoptosis. The immunomodulatory activity of cyclosporine A is used in the treatment of immune-based disorders, such as transplant rejection, psoriasis, ulcerative colitis, rheumatoid arthritis, and DED. Topical administration of cyclosporine A has been
shown to increase tear fluid secretion, possibly by promoting the local release of parasympathetic nervous system–associated neurotransmitters. The beneficial effects of cyclosporine A treatment in DED are well established; however, it is clear that many patients with DED do not show a consistent therapeutic response to topical cyclosporine A. The cumulative findings of several clinical trials indicate that long-term treatment with cyclosporine A, 0.05%, ophthalmic emulsion can yield positive results with regard to objective and subjective findings, including corneal surface staining, Schirmer test with anesthesia, blurred vision, and frequency of artificial tear application. In addition, topical cyclosporine A treatment may be associated with a significant improvement in many of the cellular and molecular markers of disease severity. Increased frequency of topical cyclosporine A administration may be of benefit to patients refractory to the standard dosing regimen. Although higher dosing frequencies may increase treatment efficacy, some patients experience bothersome adverse effects (eg, burning or irritation) that impair medication tolerability.

Corticosteroids

Corticosteroids are steroid hormones that can be used to suppress inflammation. Corticosteroids bind to glucocorticoid receptors and inhibit the expression of pro-inflammatory molecules, promote the expression of anti-inflammatory molecules, and stimulate the apoptosis of lymphocytes. Experimental studies have demonstrated the efficacy of corticosteroids in the treatment of DED at the cellular, molecular, and clinical levels. Clinical trials have demonstrated the efficacy of topical corticosteroid treatment at diminishing symptom severity and minimizing ocular surface staining. Systemic corticosteroid administration may also be effective in the treatment of severe acute dry eye refractory to more traditional treatment modalities. Unfortunately, long-term topical or systemic corticosteroid use is associated with deleterious adverse effects, such as ocular hypertension, cataracts, and opportunistic infections. Repetitive short-term pulsatile administration of topical corticosteroids is a promising method of harnessing their beneficial effects, while minimizing the risk of adverse events.

Tetracycline Derivatives

Tetracycline derivatives are unique in that they possess antibacterial and anti-inflammatory properties. They exert antibacterial activity by reversibly binding to the bacterial ribosome and inhibiting the production of proteins. Tetracycline derivatives have been noted to possess immunomodulatory properties at submicrobial doses. Experimental investigations have demonstrated that the tet-
racycline derivative doxycycline can inhibit c-Jun N-terminal kinase and extracellular signal–related kinase mitogen-activated protein kinase signaling in epithelial cells of the ocular surface exposed to hyperosmolar stress, downregulating the expression of CXCL8 and proinflammatory cytokines IL-1β and TNF. Doxycycline inhibits the activity of MMPs (eg, MMP-9) and supports ocular surface integrity. In addition, the tetracycline-derivative minocycline inhibits the expression of cell-associated proinflammatory molecules, including MHC class II. A novel topically applied liposome-bound form of tetracycline has shown some promise in the treatment of experimental DED. The anti-inflammatory benefits of orally administered tetracycline derivatives have been used in the treatment of chronic immunomediated diseases, including dry eye secondary to ocular rosacea and blepharitis. Despite extensive evidence from experimental trials indicating the potential benefits of administration of tetracycline derivatives in the treatment of DED, there is limited clinical evidence of their efficacy.

**Essential Fatty Acids**

Essential fatty acids (EFAs) are biologically necessary fatty acids (FAs) that must be ingested because they cannot be synthesized de novo by the human body. Humans require 2 EFAs for optimal health, -3 (α-linolenic acid) and -6 (linoleic acid) FAs. Essential fatty acids are the precursors of eicosanoids (prostaglandins, prostacyclins, thromboxanes, and leukotrienes) that modulate immune responses. Omega-3 FAs are generally classified as anti-inflammatory, while -6 FAs are generally pro-inflammatory. Omega-3 FAs block the production of proinflammatory eicosanoids (prostaglandin E2 and leukotriene B4) and cytokines (IL-1 and TNF). The anti-inflammatory effects of -3 FAs have been used in the treatment of immunomediated disorders, including Sjögren syndrome. Investigations on the use of EFAs in the treatment of DED have produced conflicting results; however, most of the available evidence suggests that administration of EFAs, particularly -3 FAs, can lessen DED severity. Several clinical trials have investigated the systemic administration of various EFAs and demonstrated beneficial effects with regard to the signs and symptoms of DED. Topical administration of -3 FAs significantly decreased ocular surface staining, cytokine expression, and immune cell infiltration in an experimental model of murine dry eye. Topical administration of resolvin E1, an -3 FA derivative, increased tear production, helped maintain ocular surface integrity, decreased cyclooxygenase 2 expression, and decreased immune cell infiltration in experimental dry eye. Available data suggest that EFAs can ameliorate DED; however, more evidence is needed to identify the most efficacious forms and doses of EFAs.

**Novel Therapeutics**

The past several years have yielded a veritable explosion of new information about the immunopathogenesis of DED. The successful application of cyclosporine in the clinical management of DED has implicated the inflammatory mediators of DED as promising targets for therapeutic intervention. A thorough review of the therapeutic agents being investigated is beyond the scope of this article. Our laboratory has been involved in the evaluation of anti-inflammatory agents using a short-term experimental model of murine dry eye. Positive results have been reported using various therapeutic agents that target inflammatory mediators, including CCR2, very late antigen 4, and IL-17, to name a few. Other laboratories have reported positive results using medications that inhibit inflammation. Needless to say, interest in evaluating potential therapeutic agents for DED has increased exponentially.

In conclusion, the evidence implicating inflammation in the pathogenesis of DED has opened new avenues for the treatment of this complex disorder. The successful application of anti-inflammatory medications in the treatment of DED provides hope for the millions of individuals who daily experience this deleterious condition. We anticipate that the advent of novel immunomodulatory agents will herald a new era of DED treatment.

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