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Autoimmunity in the Pathogenesis and Treatment of Keratoconjunctivitis Sicca

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Abstract

Dry eye is a chronic corneal disease that impacts the quality of life of many older adults. keratoconjunctivitis sicca (KCS), a form of aqueous-deficient dry eye, is frequently associated with Sjögren's syndrome and mechanisms of autoimmunity. For KCS and other forms of dry eye, current treatments are limited, with many medications providing only symptomatic relief rather than targeting the pathophysiology of disease. Here, we review proposed mechanisms in the pathogenesis of autoimmune-based KCS: genetic susceptibility and disruptions in antigen recognition, immune response, and immune regulation. By understanding the mechanisms of immune dysfunction through basic science and translational research, potential drug targets can be identified. Finally, we discuss current dry eye therapies as well as promising new treatment options and drug therapy targets.

Keywords

Dry eye; Autoimmunity; Keratoconjunctivitis sicca; Sjögren's disease; Pathogenesis; Treatment; Immune regulation; Humoral immunity

INTRODUCTION

Dry eye is a significant ocular disease that affects up to 35 % of the population aged 65 years and over [1]. Dry eye is a dysfunction of the nasolacrimal unit consisting of the nasolacrimal glands, corneal surface, and eyelids that results in an insufficient tear film. Patients experience ocular irritation often described as burning, gritty sensation, or dryness. The symptoms generally vary during the day and are often worse at night. Other symptoms

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include photophobia, itching, mucous accumulation, and tearing. Dry eye poses a significant problem, as it can lead to complications such as visual impairment, corneal ulceration, infection, anxiety, depression, and decreased quality of life.

Dysfunction in dry eye can be classified by mechanism: aqueous-deficient dry eye, evaporative dry eye, or mixed mechanism. In aqueous-deficient dry eye, the lacrimal duct produces an insufficient volume of tears, either due to dysfunction or destruction of the lacrimal glands; the latter group is mostly associated with autoimmune diseases such as Sjögren's disease. In evaporative dry eye, poor tear quality and tear film hyperosmolarity stem from defects such as meibomian (sebaceous) gland dysfunction, lagophthalmos (inability to close the eyelids completely), or decreased blink function [2].

Aqueous-deficient dry eye is also referred to as keratoconjunctivitis sicca (KCS). Henrik Sjögren first described KCS in 1933 as ocular findings in patients with primary Sjögren's disease. The prevalence of KCS is 4 % in adults over age 65. KCS is generally insidious in onset, presenting more commonly in females and Caucasians. In addition to Sjögren's disease, other causes of KCS include age-related atrophy of secreting glands and drug-induced KCS. Specifically, KCS has been associated with the use of beta-blockers, diuretics, antihistamines, and antidepressant drugs [1]. In this review, we focus on Sjögren's-associated KCS, and the autoimmune-based mechanisms and treatments for keratoconjunctivitis sicca.

MECHANISMS OF PATHOGENESIS IN AUTOIMMUNE-MEDIATED KCS

Although precise mechanisms underlying autoimmune-mediated keratoconjunctivitis sicca are not well understood, the pathogenesis of keratoconjunctivitis sicca is likely multi-factorial with genetic and environmental components contributing to autoimmunity. Research has revealed potential mechanisms of dysfunction and dysregulation in the physiologic immune response resulting in the pathogenesis of KCS. In this review, we emphasize genetic susceptibility to the disease as well as disruptions in antigen recognition, immune response, and immune regulation, in the context of autoimmune-mediated KCS.

Genetic Susceptibility

Major histocompatibility complex (MHC) class II molecules have long been implicated in autoimmune diseases such as Sjögren's disease. On a transcriptional level, certain human leukocyte antigen (HLA) genes, such as HLA-DRβ1, encode specific MHC class II molecules and are upregulated in patients with Sjögren's disease [3]. The upregulation of such HLA alleles is thought to genetically predispose individuals to Sjögren's disease and thus has utility for clinical diagnosis. To our knowledge, there are no specific HLA genes that predispose individuals to non-Sjögren's-associated KCS.

Antigen Recognition

Autoantibodies—Antibodies against self-antigens are a well-established mechanism for antigen recognition and autoimmunity. Autoantibodies have long been used as diagnostic markers for Sjögren's disease. In particular, anti-Ro/SSA, anti-La/SSB, and anti-nuclear antibodies (ANA) are often detected at high levels in patients with Sjögren's disease.

Interestingly, autoantibodies can potentially be used to discriminate between Sjögren's-associated KCS versus other causes of aqueous-deficient dry eye. Compared to dry eye patients without Sjögren's disease, anti-Ro and anti-La antibodies have only been detected in Sjögren's-associated KCS [4]. New antibody markers for Sjögren's disease continue to be discovered and are directed against a variety of antigens, including nuclear, cytoplasmic, membrane-bound, and secreted proteins [5]. For example, NuMA (nuclear mitotic apparatus) and MCAs (mitotic chromosomal autoantigens) have recently been reported [6]. Nonetheless, only anti-Ro/SSA and anti-La/SSB antibodies are routinely used in diagnostic testing of Sjögren's disease. Notably, autoantibodies alone are unable to elicit or predict the development of autoimmune disease, since autoantibodies can be detected in healthy patients due to tolerance to self-antigens [5, 6].

Molecular Mimicry—Pathogens such as viruses can also elicit an autoimmune response in a process called molecular mimicry, whereby antigen epitopes on microbial proteins cross-react with mammalian self-antigens. It is hypothesized that molecular mimicry mediates post-viral KCS. The herpes simplex virus has been shown to react with La/SSB antigen in Sjögren's patients [7], and Coxsackie virus 2B can cross-react with the Rh60 autoantigen [8]. Interestingly, the two aforementioned viruses have also been shown to cross-react with autoantigens in systemic lupus erythematosus (SLE) patients [7, 8].

Apoptosis and Antigen Presentation—Apoptosis is a process of controlled cell death that can be used to eliminate injured or damaged cells. Apoptosis has been linked with autoimmune diseases such as Sjögren's disease [9] and SLE [10]. In the context of autoimmune disease, apoptosis-produced cell debrism such as DNA and/or RNA fragmentsm likely induce autoantigens and subsequent inflammation. Interestingly, an accelerated rate of apoptosis has been observed in Sjögren's disease [9, 11, 12]. Within the eye, increased corneal epithelial cell apoptosis has been observed in both Sjögren's- and non-Sjögren's-associated KCS in a mouse model of environmentally-induced KCS [13]. These results suggest that, in addition to autoimmune-mediated KCS, apoptosis likely plays an important role in other forms of KCS such as evaporative dry eye. At present, it is unclear how autoantigens are elicited from apoptotic cell debris. In Sjögren's disease, it is hypothesized that the process of autoantigen generation involves an initial subcellular redistribution and clustering of molecules into blebs on the surface of apoptotic cells [14].

DNA and/or RNA fragments from apoptotic cells also have the ability to activate toll-like receptors (TLRs). TLRs are found on immune cells such as macrophages and dendritic cells, as well as in the gut, where they respond to pathogen-associated molecular patterns to elicit an immune response. In one of the major TLR signaling pathways, MyD88 recruits IRAK followed by downstream NF-κB-associated nuclear translocation and transcription that ultimately induces a pro-inflammatory state. Specific toll-like receptors such as TLR3, TLR7/8m and TLR9 are activated in systemic autoimmune diseases like Sjögren's disease [15]. On the corneal surface of KCS patients, increased apoptosis is observed with chromatic and small ribonuclear particles (snRNPs) likely activating TLRs [13].

In autoimmune diseases, apoptosis is regulated by key molecules, many of which have been elucidated in recent studies. IκB is a transcription factor associated with NF-κB [16], and

has recently been shown to be important in autoimmunity and inflammation in a mouse model with IκB-deficient epithelial cells, Okuma et al. demonstrated accelerated apoptosis and development of a Sjögren's-like autoimmune syndrome [17]. This suggests IκB is required for the normal time course of apoptosis. Furthermore, IκB has been shown to be regulated by STAT3, a transcription factor needed for Th17 differentiation. Th17 induces cytokines and inflammation and thus may play a critical role in autoimmune diseases such as KCS [18]. In addition, the cytokine IFN-γ has been identified as a modulator of increased apoptosis in the conjunctival epithelium [19]. In this study, Zhang et al. found that goblet cells were strongly targeted for IFN-γ-dependent apoptosis in a desiccating stress-induced mouse model of KCS (induced by scopolamine, air draft exposure, and low humidity).

Another apoptotic pathway likely involved in Sjögren's disease and KCS is death receptor Fas/Fas ligand (FasL) binding. In apoptosis, the Fas/FasL interaction activates caspases and proteinases that result in DNA fragmentation and cell death. Higher levels of Fas-positive cells and soluble FasL were detected in the serum of Sjögren's-associated KCS than in non-Sjögren's KCS patients [20]. Although this study suggests a role for Fas/FasL and apoptosis in Sjögren's-associated KCS, a direct correlation has not been established between increased serum Fas/FasL and increased rate of apoptosis. Future research is needed to further elucidate the role of Fas/FasL binding and its mechanism of action in autoimmune-mediated apoptosis.

Antigen Presenting Cells—In KCS, antigens derive from multiple sources—autoantigens, molecular mimicry, and apoptosis. These antigens are presented to immature antigen-presenting cells (APCs), which are then activated by major histocompatibility complex (MHC) class II cell surface receptors. Mature APCs then present antigen to T cells to generate an inflammatory and immune response.

The process of antigen presentation in KCS appears to be altered, at least in some cases, at the step involving MHC class II and other costimulatory molecules. Within the conjunctival epithelium of patients with Sjögren's disease, specific MHC II molecules such as HLA-DR are upregulated [20]. Interestingly, this HLA-DR upregulation has been observed in Sjögren's- and non-Sjögren's-associated KCS patients [21]; however, significantly higher levels of HLA-DR are expressed in Sjögren's-associated versus non-Sjögren's-associated KCS. These data suggest that HLA-DR upregulation has a role in the pathophysiology of aqueous-deficient dry eye and, in particular, Sjögren's-associated KCS. Because of its upregulation, HLA-DR has been used as a marker for active disease in KCS, as reduced HLA-DR expression has been observed in experimental testing of the efficacy of pharmacologic treatments such as pranoprofen and cyclosporine A for dry eye [22, 23].

Also, in the cornea, MHC class II molecules show distinct localization patterns that are disrupted in KCS. Endogenous MHC class II-expressing and non-expressing cells localize to the corneal periphery, while, in the central corneal epithelium, only MHC II non-expressing cells are detected [24]. However, in the conjunctival epithelium of patients with KCS, MHC II molecules are overexpressed [25, 26] ,and APCs, notably dendritic cells, are significantly upregulated in the central corneal epithelium [27]. Similarly, MHC class II molecules are upregulated in the salivary glands of Sjögren's patients [28].

In addition, costimulatory molecules such as CD40 and B7 are upregulated in corneal inflammation as well as Sjögren's-associated KCS [20, 29]. With ongoing injury to the ocular surface in KCS, MHC class II and costimulatory molecules are repeatedly triggered, further perpetuating the cycle of antigen recognition, immune response, and inflammation [29]. How exactly MHC II and other costimulatory molecules are upregulated on the ocular surface remains unknown. A recent study has revealed several molecular pathways for control of MHC class II presentation via regulation of transcription and protein translocation to the cell membrane. These pathways involve TGF-β, the actomyosin cytoskeleton, and regulation by GTPases [30]. The role of TGF-β in MHC II presentation is particularly intriguing given the presence of endogenous TGF-β in lacrimal tears [31], increased activity of TGF-β in dry eye, and even higher TGF-β activity in Sjögren's-associated KCS [32]. In a mouse model of dry eye, disruption of TGF-β was found to suppress APC maturation in the cornea, leading to an improvement in dry eye phenotype and in conjunctival inflammation [33, 34]. Furthermore, factors that regulate TGF-β have been shown to be involved in the pathogenesis of Sjögren's-like KCS in mice [35]. Thus, the TGF-β signaling pathway poses an intriguing drug therapy target for the treatment of KCS.

Immune Response

Cell-mediated Immunity—It is clear that a disruption in cell-mediated immunity is important in the pathogenesis of autoimmune diseases such as Sjögren's disease, as mice with defective T cell development acquire symptoms of Sjögren's disease as well as anti-Ro/SSA and anti-La/SSB antibodies [36]. Moreover, the introduction of desiccating stress in mice has been shown to induce T cell-mediated inflammation, specifically in the cornea, conjunctiva, and lacrimal gland. In this study, primed T cells were adoptively transferred to T cell-deficient nude mice and produced a similar KCS-type inflammatory response [37]. T cells and cell-mediated immunity are important in the inflammatory pathway in KCS following antigen presentation.

Humoral Immunity—The humoral immune response is mediated by B cells, which produce antibodies targeted against pathogenic antigens. B cell dysfunction and the resultant disruption of host immune tolerance have been observed in autoimmune diseases such as SLE, rheumatoid arthritis, type I diabetes, and multiple sclerosis [38]. B cell dysfunction has also been implicated in the pathogenesis of Sjögren's disease [39]. In the NOD mouse model of Sjögren's disease, mice lacking mature B cells did not develop lacrimal and salivary gland dysfunction [40]. This suggests that B cells are necessary for the development of Sjögren's disease. B cell hyper-reactivity followed by hypergammaglobulinemia have been observed in Sjögren's disease [41]. Furthermore, upregulation of B cell activating factors, BAFF and APRIL, has been detected in the lacrimal glands of Sjögren's patients [42, 43]. BAFF (BLyS or B-lymphocyte stimulator) is a B cell activating factor of the tumor necrosis factor family found to be significantly overexpressed in salivary glands of Sjögren's disease patients [44] with the effect of preventing the apoptosis of autoreactive B cells [45]. As for APRIL (a proliferation-inducing ligand), it is yet to be determined whether its upregulation induces B cell hyperactivity and hypergammaglobulinemia. Interestingly, immunoglobulin is sufficient to induce KCS, as immunoglobulin serum derived from a KCS mouse injected into a nude-recipient mouse produced KCS and inflammation [21]. Furthermore, goblet cell

apoptosis was observed in the KCS-immunoglobulin recipient mice [21], thus illustrating the complexity of the pathogenesis of immune dysfunction in autoimmune disease.

Immune Regulation

Helper T cells—Helper or effector T cells are activated after APC stimulation and facilitate cytokine secretion. In KCS, research has focused on the effector T cells, T_H1 and T_H17 [32]. T_H17 induces the secretion of IL-17 in response to TGF-β or IL-6, which then stimulates the production of pro-inflammatory cytokines and matrix metalloproteinases [46]. Matrix metalloproteinases are upregulated in the lacrimal and salivary glands in Sjögren's disease [47], and significant tissue injury and destruction can result from their activity [48]. The T_H17-centric cytokine IL-17 has been analyzed in the tear film, revealing highest levels in Sjögren's-associated KCS as well as increased levels in non-Sjögren's-associated KCS versus control subjects [49]. Interestingly, the induction of IL-17A into murine salivary glands was sufficient to induce a Sjögren's-like phenotype of reduced salivary function, inflammation, and positive antibody markers such as anti-ANA [50]. T_H17 has been implicated in other autoimmune diseases such as Crohn's disease [51] and collagen-induced arthritis [52]. Thus, the regulation of pro-inflammatory cytokines and matrix metalloproteinases has a significant role in KCS that results in tissue injury and reduced function of exocrine glands. From this work, drug targets such as localized anti-IL17 have been proposed [50].

Regulatory T cells—Regulatory T cells (Tregs) are thought to maintain immune tolerance to autoimmune antigens. Correspondingly, dysfunction of regulatory T cells is observed in autoimmune diseases such as Sjögren's disease, SLE, and rheumatoid arthritis [53]. Notably, Tregs are important for the development of Sjögren's-associated KCS: in a mouse model of KCS using Treg-deficient nude mice, T cells from KCS-primed mice were adoptively transferred, resulting in the development of Sjögren's-like disease even without a desiccating stress trigger [37]. This study suggests that Treg deficiency could predispose to Sjögren's disease and KCS. Interestingly, T_H17 cells implicated in the pathogenesis of KCS have been shown to be resistant to Treg-mediated suppression [54]. Correspondingly, a demonstrated imbalance between Treg cells and IL-17, with a disproportionate increase in IL-17, in mild to moderate inflammation in Sjögren's disease has been hypothesized to lead to tissue injury and pathology [55]. The imbalance between IL-17 and Treg cells provides another focus for potential therapies to alter the immune response in Sjögren's-associated KCS.

TREATMENTS FOR KCS

Our understanding of the mechanisms of dysfunction of the immune system has guided the development of drug therapy for KCS. However, treatments for dry eye, particularly in the context of autoimmune dysfunction, remain limited. Ongoing research in autoimmune-mediated KCS is critical, with the hope of elucidating novel drug targets and therapies for this chronic and debilitating eye disease.

Thus far, treatments for autoimmune-based KCS have been targeted toward stimulation of tear secretion, anti-inflammatory agents, artificial tear replacement, and tear film

maintenance. As a first-line treatment option, artificial tears can provide temporary, symptomatic relief. Frequent topical application hinders its use for long-term treatment, and, furthermore, artificial tear replacement does not address the pathophysiology of dry eye disease. Tear secretion stimulators, such as cyclosporine A and cevimeline, are available and will be discussed below. Other drugs stimulating tear secretion include pilocarpine and diquafosol (approved for treatment in Japan). Also, anti-inflammatory agents have been assessed for the treatment of dry eye. Topical corticosteroids, although likely effective in alleviating the symptoms of dry eye [56, 57], are not recommended for long-term therapy due to complications such as increased intraocular pressure and cataract formation. Finally, topical NSAIDs have also been evaluated for dry eye treatment, but, unfortunately, topical NSAIDs are not as effective at providing symptomatic improvement versus topical corticosteroids or artificial tear replacement alone [57].

Cyclosporine A—Cyclosporine A is a generally well-tolerated treatment strategy for dry eye that has been FDA-approved for over a decade. Although cyclosporine is an immunosuppressive agent when administered systemically, topical cyclosporine acts as a partial immunomodulator in the eye and has been used for a wide range of ocular diseases with an inflammatory component, such as dry eye, posterior blepharitis, post-LASIK dry eye, atopic keratoconjunctivitis, and graft-versus-host disease [58]. In two mouse models of Sjögren's disease, cyclosporine has been shown to increase tear production [59]. In agreement with mouse models, randomized controlled trials in patients with moderate to severe dry eye showed improved ocular discomfort, less blurred vision, and improved Schirmer test scores with cyclosporine [60].

Another mechanism of action of cyclosporine in the treatment of dry eye is the inhibition of apoptosis. In a dry eye mouse model and in human conjunctival epithelial cells, cyclosporine reduced apoptosis as well as the number of infiltrating lymphocytes [61, 62]. In NOD mice, cyclosporine reduced Fas ligand expression in infiltrating lymphocytes [59]. In addition to cyclosporine, other means to inhibit apoptosis have been proposed as potential treatment modalities; for example, local Fas ligand transfer via adenoviral vectors [63] or the use of the anti-apoptotic agent D-beta-hydroxybutyrate [64] have been suggested as potential drug therapies.

Cevimeline—Cevimeline activates muscarinic M3 receptors and has been used to treat xerostoma (dry mouth) in patients with Sjögren's disease. In randomized prospective double-blinded trials to evaluate the efficacy of cevimeline in KCS, the cevimeline treatment arm had improved tear biometrics, as measured by Schirmer testing, rose Bengal and fluorescein staining, and tear break-up time, as well as subjective patient symptom reporting [65–67]. Although promising in terms of efficacy, systemic cevimeline has been associated with side effects of nausea, abdominal pain, sweating, headache, dizziness and cardiac arrhythmias, resulting in a withdrawal rate of 14–19 % from these clinical trials [66, 67].

Other potential drug targets

Rituximab—Rituximab is a monoclonal antibody directed against CD20 that targets B cells. Although rituximab has been studied in the treatment of systemic manifestations of

Sjögren's disease, less is known about the role of rituximab specifically in Sjögren's-associated KCS. Other B cell-depleting therapies, such as interferon-alpha and anti-B-cell activating factor (BAFF), have been investigated, and short-term benefit has been demonstrated with both [68]. Success with rituximab and other B cell depleting therapies suggests that B cells play an important role in Sjögren's disease, and, as a general strategy, B cell-targeted therapies have shown potential for treatment of KCS.

Gene therapy—Gene therapy is a promising approach for targeted and long-term treatment with unique advantages of avoiding multiple daily applications of eye drops and side effects of chronic medication use. In gene therapy, a gene of interest is introduced into the organ of choice by a viral vector. In the case of dry eye, the tissues such as the lacrimal gland [69] and the corneal epithelial surface have been targeted in mouse models with some success. In a mouse model for radiation-induced dry eye, pretreatment with a viral vector to express erythropoietin improved the quality of the ocular surface as well as the exocrine function of lacrimal and salivary glands [70]. In another mouse model for dry eye, a plasmid with the MUC5AC gene, encoding glycoprotein mucin 5AC, was introduced onto the ocular surface by cationized gelatin-based nanoparticles. Results showed that the treatment was well tolerated with a favorable reduction in inflammation and improved tear production [71]. While currently in the preliminary stages, gene transfer has shown exciting potential for the treatment of dry eye.

CONCLUSIONS

In keratoconjunctivitis sicca, autoimmunity plays a large role, particularly in Sjögren's-associated KCS. While the complexity of the pathogenesis of disease has hindered progress in treatments for autoimmune-mediated KCS, research has identified key steps in the immune response that produce dysregulation, tissue injury, and symptomatic disease. Immune dysregulation is likely multi-factorial, with contributing factors including genetic susceptibility and dysfunction of antigen recognition, immune response, and/or immune regulation. The combination of basic science and translational and clinical research has elucidated numerous potential drug targets for KCS, a disease that currently has limited treatment options. As a chronic disease, KCS and its prevalence are expected to increase with the aging population. Thus, the development of new drug therapies for KCS will yield great benefit in the coming years.

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