Published in final edited form as:
Exp Eye Res. 2013 December ; 117: . doi:10.1016/j.exer.2013.08.013.

T helper Cytokines in Dry Eye Disease

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Abstract

Dry eye is an inflammatory disease that results from activation of innate inflammatory pathways in resident ocular surface cells, as well as cytokines produced by recruited T helper (Th) cells. Cytokines produced by the infiltrating Th cells alter the normal cytokine balance on the ocular surface and cause ocular surface epithelial pathology. Changes in levels of Th cytokines on the ocular surface have been measured in dry eye and the biological effects of these cytokines have been documented in experimental culture and mouse model systems. The Th2 cytokine IL-13 has a homeostatic role in promoting goblet cell differentiation. In contrast, The Th1 cytokine IFN-γ antagonizes IL-13 and promotes apoptosis and squamous metaplasia of the ocular surface epithelia. The Th17 cytokine, IL-17 promotes corneal epithelial barrier disruption. The ocular surface epithelium expresses receptors to all of these Th cytokines. Therapies that maintain normal IL-13 signaling, or suppress IFN- γ and IL-17 have potential for treating the ocular surface disease of dry eye.

Keywords

Dry Eye; Tear Dysfunction; Inflammation; T cell; cytokine; interleukin 13; interferon gamma; interleukin 17

1.1. Introduction

It is now recognized that inflammation is a cause and consequence of dry eye disease. Decreased production of aqueous tears by the lacrimal glands or increased tear evaporation due to lipid deficiency or decreased blink rate can result in changes in tear composition that promote inflammation on the ocular surface and lid margins. Elevated tear osmolarity has been measured in all types of tear dysfunction (Tomlinson et al., 2006). Exposure of ocular surface epithelium to elevated osmolarity activates stress signaling pathways, including the JNK and NFκB pathways that promote production of inflammatory molecules, including cytokines, chemokines and matrix metalloproteinases (MMPs). Alternatively, ocular surface and lacrimal gland inflammation may develop in systemic autoimmune disease due to infiltration of these tissues with activated T lymphocytes (Stern et al., 2013).

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The ocular surface has resident lymphoid cells, including dendritic cells, natural killer (NK) cells, B cells and conventional and γδ T cells that suppress (Zhang et al., 2012; Hattori et al., 2012; Khandelwal et al., 2013; Zhang et al., 2013) or promote (Zhang et al., 2012) immune responses. A major function of these cells is to defend against the variety of microbial agents that populate or infect the cornea and ocular surface (Knop and Knop, 2005; Ueta and Kinoshita, 2012). Conjunctival intraepithelial lymphocytes, such as NK or NKT cells, may also have a homeostatic function on the ocular surface by supporting differentiation of conjunctival goblet cells that secrete gel-forming mucin into the tears that has key stabilizing and protective functions (de Paiva et al., 2010b).

1.2. T helper Subsets

The immune response to foreign antigens requires a perfect coordination between sensor and effector cells. $CD4^+$ T cells, also known as T helper (Th) cells, play a central role in immune protection. Naïve conventional $CD4^+$ T cells have open to them at least 4 distinct fates that are determined by the pattern of signals they receive during antigen presentation. These 4 populations are Th1, Th2, Th17 and induced regulatory (iTreg) cells (Mosmann et al., 1986; Mosmann, 1992; Mosmann and Coffman, 1989; Mosmann and Sad, 1996; Zhu and Paul, 2008; Zhu and Paul, 2010). The cytokines secreted by these Th populations modulate various immune responses and are responsible for their functional roles.

Th1 cells secrete IFN-γ that activates macrophages that function in eradicating intracellular microorganisms, such as mycobacteria. Th1 cells also promote cytotoxic T cell development and delayed type hypersensitivity reactions (Mosmann et al., 1986; Mosmann, 1992; Mosmann and Coffman, 1989; Mosmann and Sad, 1996). Hence, Th1 cells are pro-inflammatory and may be involved in the pathogenesis and maintenance of some autoimmune diseases (Dardalhon et al., 2008).

Th2 cells produce IL-4, IL-5 and IL-13, cytokines that mediate immunity against parasitic infestations, and are pivotal in the development of atopic diseases, including seasonal allergy, asthma and atopic dermatitis/keratoconjunctivitis. IL-4 and IL-13 promote IgE switching by B cells (Mosmann et al., 1986; Mosmann, 1992; Mosmann and Coffman, 1989; Mosmann and Sad, 1996). IL-5 promotes activation and immunoglobulin secretion by B-cells and also eosinophil activation (Lee et al., 2013). IL-13 can also promote fibrosis (Doherty et al., 2007).

Th17 cells secrete IL-17, which induces production of pro-inflammatory molecules (cytokines, chemokines and MMPs) and recruits neutrophils (Bettelli et al., 2006; Bettelli et al., 2007). Th17 cells are involved in the early response to numerous extracellular pathogens, including bacteria and fungi, and have been found to be involved in autoimmunity and tissue inflammation (Chen and O'Shea, 2008).

It is thought that naïve CD4 cells, in the presence of TNF-α and IL-6, develop into Th22 cells that secrete IL-22 and TNF-α. These cells may be involved in epidermal immunity and remodeling in inflammatory skin diseases such as psoriasis, microbial infections, inflammatory and autoimmune diseases (Akdis et al., 2012; Eyerich et al., 2009; Kagami et al., 2010; Muhl et al., 2011; Qiao et al., 2011; Ryan-Payseur et al., 2011; Sanos and Diefenbach, 2013; Shao et al., 2012; Tian et al., 2013; Wolff et al., 2012; Zhang et al., 2011a).

Other Th subsets have a role in tolerance, rather than immunity. These include Tr1 cells (secreting IL-10), Th3 cells (secreting TGF-β), and Treg cells (secreting IL-10 and TGF-β) (Andolfi et al., 2012; Ankathatti et al., 2012; Battaglia et al., 2006; Carrier et al., 2007a; Carrier et al., 2007b; Zhu and Paul, 2008).

1.3. Th Cells in Dry Eye

There is a growing body of evidence documenting the presence and activity of $CD4^+$ T cells in dry eye disease. Biopsies taken from patients with Sjögren Syndrome (SS) early in the course of the disease have shown lymphocytic infiltration in the lacrimal gland and activated T cells in the conjunctiva. (Calonge, 2001; Jones et al., 1994; Kunert et al., 2000; Pflugfelder et al., 1999; Solomon et al., 2001a; Stern et al., 2002). Mouse models of dry eye have provided the opportunity to investigate the role of specific T cell subsets in the pathogenesis of dry eye.

A great body of evidence supporting the pathogenicity of $CD4^+$ T cells in dry eye comes from animal studies using either autoimmune (spontaneous) or induced animal models. Definitive studies using adoptively transferred CD4+ T cells from mice exposed to desiccating stress to naïve immunodeficient mice performed by our group established a direct pathogenic role for $CD4^+$ T cells (Niederkorn et al., 2006). However, the transfer of $CD4^+$ T cells into competent mice did not induce disease unless regulatory T cells were depleted (Niederkorn et al., 2006). Additional animal and human studies have shown that dry eye elicits mixed Th1 and −17 responses in the conjunctiva (Chauhan et al., 2009; de Paiva et al., 2009). Both Th subtypes have been found to have a pathogenic role (Chen et al., 2011; de Paiva et al., 2007a; de Paiva et al., 2009). Studies dissecting individual contributions of Th1 and Th17 have been performed [(Coursey et al., 2012) and manuscript submitted].

Dry eye syndrome has a myriad of clinical presentations, but it is frequently accompanied by corneal barrier disruption and loss of conjunctival goblet cells. Indeed, breakdown of corneal barrier is one of the hallmarks of dry eye disease and it is clinically characterized by increased uptake of fluorescent tracers, such as sodium fluorescein in human subjects. Using an environmentally induced dry eye model, our group has shown that matrix metalloproteinase 9 (MMP-9) is responsible for proteolytic degradation of tight junctions in the apical corneal epithelium, facilitating dye penetration into cornea (Pflugfelder et al., 2005). Corneal barrier disruption is accompanied by increased infiltration of $CD4^+$ T cells in the conjunctiva; loss of PAS+ filled goblet cells and increased infiltration of CD11b+ cells into the cornea (Chauhan et al., 2009; de Paiva et al., 2006; de Paiva et al., 2007a).

Migration of CD4+ T cells into the conjunctival and cornea in dry eye disease may be modulated by chemokine ligands produced by the surface epithelium that increase in dryness. Pathogenic CD4 cells that infiltrate the ocular surface tissues express receptors to these ligands (de Paiva et al., 2009; Yoon et al., 2007; Yoon et al., 2010; Dohlman TH et al., 2013). It has also been shown that manipulation of afferent (migration of dendritic cells from the ocular surface to the regional lymph nodes) or efferent (migration of differentiated CD4+ T cells from the nodes to the cornea and conjunctiva) can ameliorate development of dry eye disease (Coursey et al., 2012; Goyal et al., 2009; Lee et al., 2011; Sadrai et al., 2012; Schaumburg et al., 2011) indicating that therapeutic strategies that interfere with various points in this immune circle may have clinical significance. As a matter of fact, cyclosporine A 0.01 % emulsion, the only FDA-approved drug to treat dry-eye disease has been shown to modulate several arms of the immune response by decreasing human leukocyte class II antigen (HLA-DR) expression in conjunctiva of dry eye patients (Baudouin et al., 2002; Brignole et al., 2000; Brignole et al., 2001) and decreasing expression of IL-17A and IFN-γ in conjunctiva of animals after desiccating stress (de Paiva et al., 2009).

Herein we review the association with and potential function of Th cytokines in dry eye disease.

2.1. Th2

The signature Th2 cytokines, IL-4 and IL-13, bind to heterodimeric receptors that share the IL-4Rα1 subunit. IL-4 binds to the type I IL-4R complexes, composed of IL-4Rα and γc subunits (Hershey, 2003). Type I receptors are expressed by hematopoietic and mucosal epithelial cells. Type II IL-4R complexes are composed of IL-4Rα and IL-13Rα1. They are also present on hematopoietic and non-hematopoietic cells and bind to both IL-4 and IL-13. Both receptors are present in conjunctival epithelium (Figure 1). A second IL-13 receptor, IL-13Rα2, exclusively binds IL-13 and has been found to serve as a decoy receptor (Wilson et al., 2011). We have previously found expression of the IL-13Rα1 in the conjunctival epithelium, with the strongest expression in goblet cell rich areas Figure 1 (de Paiva et al., 2010b).

IL-4 and IL-13 both utilize the JAK–signal transducer and activator of transcription (STAT) pathway, specifically STAT6. Signaling is initiated by phosphorylation of IL-4Rα and JAK1, leading to the recruitment, phosphorylation and activation of STAT6. Activated STAT6 dimers translocate to the nucleus, bind specific canonic DNA elements and initiate transcription of downstream genes (Hershey, 2003).

Both IL-4 and IL-13 have been detected in human (Carreno et al., 2010; LaFrance et al., 2008; Lam et al., 2008; Weaver et al., 2007a) and mouse tears (Corrales et al., 2007) In one study, IL-13 was detected in all tear samples, while IL-4 was detectable in only 50% and the average concentration of IL-13 was twice as high as IL-4 (Carreno et al., 2010; Corrales et al., 2007). The effects of dry eye on tear concentration IL-4 has not been studied. In one study, there was no change in tear IL-13 concentration in patients with tear dysfunction with or without meibomian gland disease (MGD) (Lam et al., 2008). In experimental murine dry eye, IL-13 significantly decreased in tears after 5 and 10 days in Th-1 prone C57BL/6 mice, while it increased in BALB/C mice that have been found to develop less severe corneal and conjunctival disease in response to desiccating stress (Corrales et al., 2007). IL-5 was detected in normal tears (Carreno E et al., 2010), was found to be elevated in tears of dry eye patients and correlated with their symptom severity (Massingale et al., 2009)

We have reported that intraepithelial NK cells are the major source of IL-13 on the ocular surface. Similar to airway epithelia, IL-13 released from these cells appears to modulate goblet cell density in the conjunctival epithelium, because goblet cell density decreased more than 25% in NK cell depleted mice. Goblet cell density was found to decrease by approximately 30% in STAT6 deficient mice and subconjunctival IL-13 administration prevented loss of goblet cells in mice subjected to experimental desiccating stress (de Paiva et al., 2010b). One mechanism by which IL-13 promotes goblet cell differentiation in the airway epithelium is by increasing expression the SAM-pointed domain epithelial-specific transcription factor (SPDEF) (Chen et al., 2009). SPDEF has been found to be an essential for goblet cell differentiation in tracheobronchial and gastrointestinal epithelium of mice (Chen et al., 2009; Gregorieff et al., 2009). It also appears to be involved in conjunctival goblet cells differentiation, because SPDEF −/− mice fail to develop goblet cells (Marko et al., 2013). It remains to be determined if IL-13 regulates SPDEF in the conjunctival epithelium.

In non-ocular systems, the Th1 cytokine IFN-γ has been found to antagonize IL-13 signaling by multiple mechanisms (Hershey, 2003) that include up regulation of suppression of cytokine signaling (SOCS) genes and stimulated production of IL-13Rα2. As noted below, IFN-γ was found to decrease conjunctival goblet cell density in mice; however, it is not known to what extent this is attributed to suppression of IL-13 signaling. Preliminary studies performed in our lab have found that expression of the IFN-γR and IL-13Rα2 increase in

patients with aqueous tear deficiency, both of which could suppress IL-13 signaling (Corrales and Pflugfelder, 2013). We have reported that dry eye decreases the IL-13/IFN-γ ratio (Lam et al., 2008). Treatment of experimental murine dry eye with topical cyclosporine (CsA) was found to increase the number of goblet cells (Pflugfelder et al., 2008; Strong et al., 2005), as well as the number of IL-13 producing NK cells (de Paiva et al., 2010b).

These studies suggest that IL-13 is the predominant Th2 cytokine on the normal ocular surface. It appears to have a homeostatic function in maintaining mucus secreting conjunctival goblet cells. IFN-γ can suppress IL-13 signaling by multiple mechanisms and this may be relevant to the conjunctival goblet cell loss that occurs in aqueous tear deficient dry eye where IFN-γ expression is increased.

In the non-obese diabetic (NOD) mouse model of Sjögren syndrome (SS), genetic deletion of IL-4 leads to decreased B-cell infiltration of the salivary and lacrimal glands, as well as preservation of glandular secretory function. These findings suggest that IL-4 promotes B-cell proliferation in this model (Nguyen and Peck, 2009). IL-4 has also been implicated in the pathogenesis of the hypergammaglobulinemia that develops in SS (Giron-Gonzalez et al., 2009).

3.1 Th1 pathway

IFN-γ is the signature cytokine from Th1 cells. It is produced by NK, NKT and activated, terminally differentiated $CD4^+$ Th1+ cells although one study showed that salivary gland ductal epithelial cells can also produce IFN-γ (Ishimaru et al., 2008). Th1 cells can be identified by expression of CXCR3 and CCR5 surface receptors. IFN-γ receptor (Figure 1) has been detected in the conjunctival and corneal epithelium and CXCR3 and CCR5 ligands (CXCL-9, CXCL10 and CXCL11) have been found in tears and conjunctiva of humans and mice (Enriquez-de-Salamanca et al., 2010; Yoon et al., 2007; Yoon et al., 2010). IFN-g is a pleotropic cytokine involved in a variety of immune functions, including recruitment and polarization of naïve CD4 cells that once differentiated produce IFN-γ. IFN-γ production has an amplifying effect since its local production induces expression of IL-12 receptor (which facilitates Th-1 differentiation) and Th-1 chemokine ligands (CXCL-9, CXCL10 and CXCL11) that recruit and anchor differentiated Th-1 cells in tissues that subsequently produce IFN-γ and perpetuate the immune based inflammation in dry eye.

IFN-γ has been proposed as a biomarker for dry eye disease and Sjögren syndrome (SS) because elevated IFN-γ, either protein and/or RNA, has been detected in tears, saliva, conjunctiva, submandibular glands and blood [tears (Boehm et al., 2011; Corrales et al., 2007; de Paiva et al., 2007a; Enriquez-de-Salamanca et al., 2010; Lam et al., 2008; Massingale et al., 2009; Mrugacz et al., 2006; Riemens et al., 2012), conjunctiva (Chen et al., 2011; Chen et al., 2006; Corrales et al., 2007; de Paiva et al., 2007a; Zhang et al., 2011b) , saliva (Kang et al., 2011; Pertovaara et al., 2006), lacrimal (de Paiva et al., 2010a; Hayashi et al., 2012; Jie et al., 2010; Ogawa et al., 2002; Pelegrino et al., 2012; Rahimy et al., 2010b; Viau et al., 2011) submandibular glands (Brookes et al., 1995; Hayashi et al., 2012; Koarada et al., 2006; Kohashi et al., 2008; Mrugacz et al., 2006), and blood (Hagiwara et al., 1998; Szodoray et al., 2008)] Evidence from mouse models and human SS patients indicate that IFN-γ is a relevant therapeutic target (de Paiva et al., 2007; de Paiva et al., 2011; Ogawa et al., 2002).

Increased IFN-γ concentration in tears of dry eye patients measured by ELISA was reported more than a decade ago. More sensitive immunoassays, such as Luminex and antibody microarrays used in subsequent studies have confirmed the early findings (Boehm et al., 2011; Corrales et al., 2007; Enriquez-de-Salamanca et al., 2010; Massingale et al., 2009; Mrugacz et al., 2006; Riemens et al., 2012). In addition to dry eye, elevated tear IFN-γ

concentration has also been found in patients with sicca symptoms after bone marrow transplantation (Riemens et al., 2012) and in tears of SS patients (Lam et al., 2008; Massingale et al., 2009). Among the various subsets of dysfunctional tear syndrome (DTS), those with meibomian gland disease (MGD) had lower IFN-γ concentration than those without MGD (Enriquez-de-Salamanca et al., 2010; Lam et al., 2008). Among all patients with DTS, tear IFN-γ concentration was found to correlate with corneal fluorescein staining score (Lam et al., 2008). It is possible that the inflamed lacrimal glands in patients with SS are one source for their increased tear IFN-γ.

Similar to tears (Riemens et al., 2012), increased IFN-γ has been found in saliva of SS patients and its presence correlated with severity of sicca symptoms (Kang et al., 2011). Interestingly, increased Th1/Th2 ratios was observed in more severe SS cases (Ajjan et al., 1998; Giron-Gonzalez et al., 2009; Konttinen et al., 1999), whereas increased Th-2 response correlated with milder SS (Kang et al., 2011; Mitsias et al., 2002; Pertovaara et al., 2006; van Woerkom et al., 2005). IFN-γ expression has been evaluated in minor salivary glands of human SS patients, as well as lacrimal and submandibular (SMG) gland biopsies in animal models. Virtually every mouse autoimmune model that mimics SS, or even environmentally-induced mouse dry eye models have shown increased expression of IFN-γ in submandibular and/or lacrimal glands (de Paiva et al., 2010a; Hayashi et al., 2012; Jie et al., 2010; Kohashi et al., 2008; Mitsias et al., 2002; Ogawa et al., 2002; Pelegrino et al., 2012; Rahimy et al., 2010b; Viau et al., 2011). In cultured labial salivary gland biopsies obtained from SS patients, the concentration of IFN-γ, but not IL-13, was associated with greater lymphocytic infiltration (Mitsias et al., 2002). Peck and colleagues identified a specific signature of IFN-γ inducible genes in LG and submandibular glands of C57BL/6.NOD-Aec1Aec2 (Peck and Nguyen, 2012). Increased expression of IFN-γ mRNA has also been observed in the conjunctiva, both in dry eye patients and mice with experimental dry eye (Chen et al., 2011; Chen et al., 2006; Corrales et al., 2007; de Paiva et al., 2007a; de Paiva et al., 2009; Zhang et al., 2011b).

IFN-γ is critical amplifying factor in immune reactions. Several studies have shown that treatment of glandular epithelial tissue with IFN-γ increases expression of HLA class I and II antigens in epithelial cells, CD80 and CD86 in dendritic cells and stimulates T cells to proliferate, thus, perpetuating the immune cascade (Brookes et al., 1995; Clark et al., 1994; De Saint et al., 1999; Manoussakis et al., 1999; Saito et al., 1993; Tsubota et al., 1999; Tsunawaki et al., 2002). Exposure of cultured glandular acini to IFN-γ led to breakdown of tight-junction proteins and increased epithelial apoptosis (Ewert et al., 2010; Katsiougiannis et al., 2010). It has also been shown that IFN-γ significantly decreases epithelial mucin expression (Albertsmeyer et al., 2010).

Recently, strategies to neutralize IFN-γ have been found to inhibit development of corneal and conjunctival epithelial disease in experimental dry eye. Neutralization of NK cells, early producers of IFN-γ (NK cells) following desiccating stress was found to decrease corneal fluorescein staining and inflammatory cytokine expression in the cornea and conjunctiva (Chen et al., 2011; Zhang et al., 2012) and also to decrease the Th-17 response (Zhang et al., 2012). IFN-γ KO mice are resistant to dry-eye induced goblet cell loss; reconstitution of these mice with exogenous IFN-γ induced the same changes observed in wild-type mice after desiccating stress, induced goblet cell loss and increased expression of cornified envelope precursor proteins by glandular the ocular surface epithelium (de Paiva et al., 2007a). Mice that received subconjunctival injections of anti- IFN-γ antibody showed decreased corneal and conjunctival apoptosis (Zhang et al., 2011b; Zhang et al., 2011c). Adoptive transfer of CD4+ T cells from anti-IFN-g treated donor mice exposed to desiccating stress were less pathogenic to immunodeficient recipient mice, yielding less corneal apoptosis and reduced loss of PAS+ filled goblet cells (Zhang et al., 2011c).

Autoimmune-prone mouse strains with IFN-γ gene deletions have been shown to have less severe dacryoadenitis (Cha et al., 2004; Pelegrino et al., 2012).

Skurkovich and Skurkovich first proposed the concept of neutralizing cytokines to ameliorate autoimmune diseases in the mid-1970s (Skurkovich and Skurkovich, 2007; Skurkovich et al., 1987; Skurkovich et al., 2005b). Their team tested efficacy of anti-IFN-γ antibodies alone or in combination with anti-TNF-α in a variety of autoimmune diseases, such as rheumatoid arthritis (RA), multiple sclerosis, psoriasis and Type 1 diabetes, among others (Nasonova et al., 2008; Sigidin et al., 2001; Skurkovich et al., 2005a; Skurkovich et al., 2005b). A small series of RA patients showed significant improvement in their clinical signs 28 days post anti-IFN-γ treatment (Sigidin et al., 2001). In the same series, another group was treated with anti-TNF-α and showed similar improvement to those treated with anti-IFN-y (Sigidin et al., 2001). Interestingly, anti-TNF-α treatment is now an FDA approved treatment for RA, while anti-IFN-γ is still under investigation for treatment of Crohn's disease (Hommes et al., 2006; Ishimaru et al., 2008).

Studies performed in mouse models of dry eye indicate that both IL-17 and IFN-γ may contribute to the development of ocular surface disease in dry eye. Consequently, neutralization of individual cytokines may only suppress disease manifestations attributable to that cytokine.

4.1. Th17

The Th17 subset produces IL-17A, IL-17F, IL-21 and IL-22 (Bettelli et al., 2006; Bettelli et al., 2007; Dardalhon et al., 2008; Stockinger et al., 2007).

TGF-β1 plus IL-6 and IL-21, the growth and stabilization factor (IL-23), and the transcription factors (STAT3, RORγt, and RORa) are involved in the differentiation of Th17 cells (Bettelli et al., 2006; Cooke, 2006; Ivanov et al., 2006; Iwakura and Ishigame, 2006; Kikly et al., 2006; Korn et al., 2007a; Korn et al., 2007b; Korn et al., 2008; Korn et al., 2009; Langrish et al., 2005; Lyakh et al., 2008; Mangan et al., 2006; Nurieva et al., 2008; Park et al., 2005; Weaver et al., 2007b).

IL-17A and IL-17F belong to the IL-17 family, which also includes IL-17B, IL-17C, IL-17D, and IL-E (IL-25). Cell type and tissue expression patterns differ greatly between the family members, but there is significant overlap in receptor binding patterns between IL-17 family members. IL-17A and IL-17F homodimers or IL-17A or IL-17F heterodimers are the principal drivers of inflammation and autoimmunity. The IL-17R family comprises five receptor subunits IL-17RA–IL-17RE. Despite considerable sequence divergence, many of the genes encoding the IL-17R family are linked, with clusters on human chromosome 3 (for IL-17RB, IL-17RC, IL-17RD and IL-17RE) and mouse chromosomes 6 (IL-17RA, IL-17RC and IL-17RE) and 14 (IL-17RB and IL-17RD) (Aggarwal and Gurney, 2002; Moseley et al., 2003). IL-17A and IL-17F both signal through IL-17RA and IL-17RC. IL-17 receptor (Figure 1) has been detected in the corneal and conjunctival epithelium (Chauhan et al., 2009).

Th17 cells can be identified by expression of CCR6 surface receptors (Coursey et al., 2012; Hirota et al., 2007; Wang et al., 2009). CCL20, the only known CCR6 ligand, is highly expressed after epithelial injury, including experimental desiccating stress (de Paiva et al., 2009; Li et al., 2011; Dohlman et al., 2013). Treatment of experimental dry eye with anti-CCL-20 antibody significantly decreased corneal fluorescein staining, infiltration of the conjunctiva with IL-17A+ cells, decrease infiltration of the cornea with CD11b+ cells and decrease expression of inflammatory cytokine and MMPs in the conjunctiva (Dohlman et al., 2013).

Dry eye has been demonstrated to cause inflammation on the ocular surface, evidenced by increased levels of inflammatory cytokines (IL-1, IL-6, TNF-α and IL-17) in the tear fluid and corneal and conjunctival epithelium, and an increased infiltration of DCs and T lymphocytes in the conjunctiva (Corrales et al., 2007; de Paiva et al., 2009; Niederkorn et al., 2006; Pflugfelder, 2004; Solomon et al., 2001a; Solomon et al., 2001b; Turner et al., 2000; Zhang et al., 2012; Zheng et al., 2009; Zheng et al., 2010). Recently, increased levels of IL-17, IL-23 and IL-6 were also found in saliva and salivary glands biopsies obtained from patients with the severe autoimmune dry eye condition, Sjögren syndrome (Katsifis et al., 2009; Nguyen et al., 2008; Sakai et al., 2008). Increased IL-17 mRNA and protein has been found in LG and SMG of mouse models of SS (de Paiva et al., 2010a; Nguyen et al., 2008; Pelegrino et al., 2012; Pitcher, III et al., 2011; Rahimy et al., 2010a; Turpie et al., 2009)

Evidence in mouse models of dry eye indicates that IL-17 stimulates production of MMP-3 and MMP-9 that contribute to disruption of corneal epithelial barrier function. Recent studies have shown that antibody neutralization of IL-17 ameliorated corneal barrier disruption in mice subjected to desiccating stress (Chauhan et al., 2009; de Paiva et al., 2009; Dohlman et al., 2013) and decreased expression of MMP-3 and −9 mRNA transcripts in the corneal epithelium (de Paiva et al., 2009) or conjunctiva (Dohlman et al., 2013), providing a definitive link between epithelial and immune cells in this process. Neutralization of IL-17 has also been found to inhibit corneal lymphangiogenesis (Chauhan et al., 2011). Memory Th cells, but not Th1 cells, were found to increase in a mouse model of chronic dry eye and these cells were capable of inducing severe corneal epithelial disease after adoptive transfer (Chen et al., 2013).

Novel therapeutic strategies aimed at inhibiting migration of $Th17^{+}CCR6^{+}$ cells to the ocular surface or production of IL-17 have been shown to decrease severity of dry eye disease in animal models of dry eye (Chauhan et al., 2009; Coursey et al., 2012; de Paiva et al., 2009; Sadrai et al., 2012; Zhang et al., 2012).

5. Conclusion

Levels of Th cytokines on the ocular surface have been found to change in dry eye and the biological effects of these cytokines have been investigated. The Th2 cytokine IL-13 has a homeostatic role in promoting goblet cell differentiation. In contrast, The Th1 cytokine IFN-γ antagonizes IL-13 and promotes apoptosis and squamous metaplasia of the ocular surface epithelia. The Th17 cytokine, IL-17 promotes corneal epithelial barrier disruption. Neutralization of IFN-γ or IL17 has been found to improve ocular surface epithelial disease.

Acknowledgments

Financial Support: NIH Grant EY11915 (SCP), an unrestricted grant from Research to Prevent Blindness, New York, NY (SCP), the Oshman Foundation, Houston, TX (SCP), the William Stamps Farish Fund, Houston, TX (SCP), Hamill Foundation, Houston, TX (SCP)

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Research Highlights

- The Th2 cytokine IL-13 has a homeostatic role in conjunctival mucus production
- Cytokines produced by T helper cells in dry eye alter the cytokine balance
- Interleukin 17 stimulates MMP production and causes corneal epithelial disease
- The Th1 cytokine IFN-γ causes apoptosis and conjunctival goblet cell loss

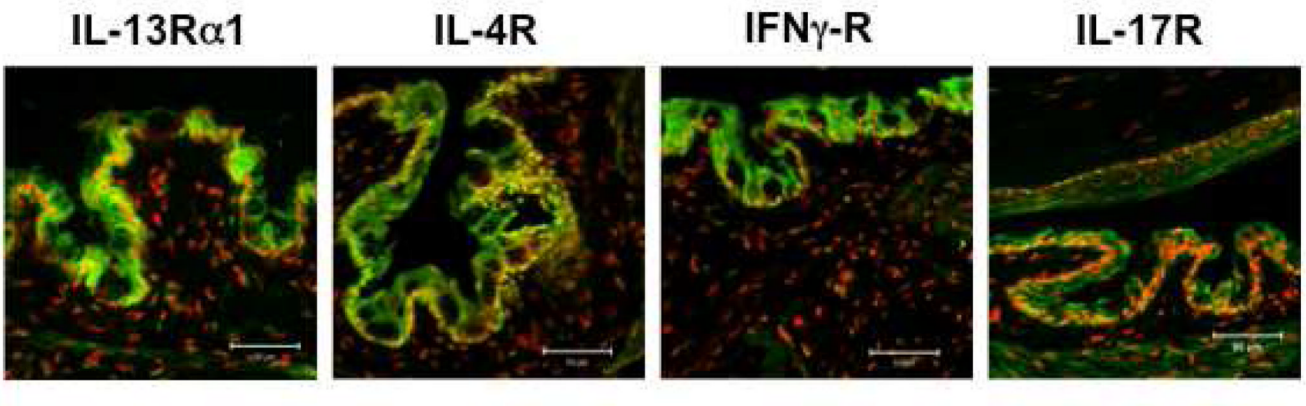

Figure 1.
Immunofluorescent staining (green) of receptors for T helper (Th) cytokines in the mouse ocular surface epithelium: Th2: IL-4Rα and IL-13Rα1; Th1: IFN-γR and Th17: IL-17RA. Nuclei are stained red with propidium iodide.

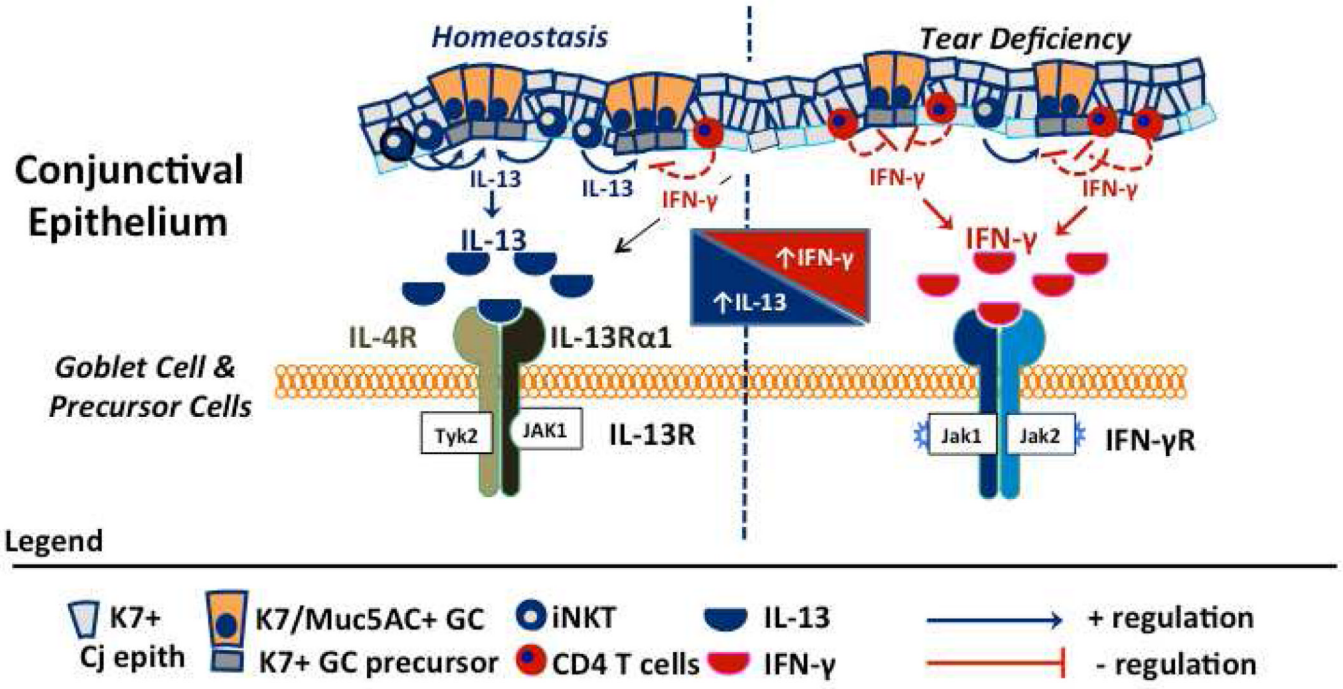

Figure 2.

Schematic summarizing balance of IL-13 and IFN-γ cytokines and receptors on the ocular surface in homeostasis and in tear deficiency. In the normal eye IL-13 produced by NKT and CD4+ cells residing in the conjunctival epithelium promotes goblet cell differentiation. Levels of IFN-γ are low. In contrast, IFN-γ expression increases in aqueous tear deficiency and IFN-γ suppresses IL-13 signaling by up regulation of suppression of cytokine signaling (SOCS) genes and stimulated production of IL-13Rα2 decoy receptor. Additionally, IFN-γ promotes cornification and apoptosis of the surface epithelium.

Table 1

Th-related cytokines in tears and conjunctiva in dry eye disease

Th Cytokine	Change in Dry Eye (tears and conjunctiva)	Associated Pathology in Dry Eye Disease
IL-4	Human: Unknown Mouse: no change	unknown
IL-13	Human: ↓ IL-13/IFN-γ ratio (Lam et al., 2008) Mouse: ↓tear concentration, ↓IL- 13/IFN-γ in C57/BL6 strain	Goblet cell loss
IFN-γ	Human: ↑ tear concentration (Lam et al., 2008; Massingale et al., 2009; (Boehm et al., 2011; Corrales et al., 2007; Enriquez-de-Salamanca et al., 2010; Massingale et al., 2009; Mrugacz et al., 2006; Riemens et al., 2012 Mouse: ↑ tear concentration (Corrales et al., 2007; de Paiva et al., 2007b) Mouse: ↑ Conjunctiva (Chen et al., 2011; Corrales et al., 2007; de Paiva et al., 2009; Zhang et al., 2011b)	Goblet cell loss Epithelial apoptosis
IL-17	Human: ↑ tear concentration (Katsifis et al., 2009) Mouse: ↑ tear concentration (de Paiva et al., 2009) Mouse: ↑ Conjunctiva (Chauhan et al., 2009; de Paiva et al., 2009)	Corneal barrier disruption; Stimulation of MMP-3 and MMP-9 mRNA by corneal epithelium