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Cornea: Window to Ocular Immunology

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Abstract

The ocular surface is continuously exposed to environmental agents such as allergens, pollutants, and microorganisms, which could provoke inflammation. However, an array of anatomical, physiological, and immunological features of the ocular surface conspire to limit corneal inflammation and endow the eye with immune privilege. A remarkable example of ocular immune privilege is the success of corneal allografts, which unlike all other forms of organ transplantation, survive without the use of systemic immunosuppressive drugs or MHC matching. This review describes the anatomical, physiological, and dynamic immunoregulatory processes that contribute to immune privilege.

Keywords

Allograft; cornea; dry eye; herpes simplex virus; immune privilege; T regulatory cells

Introduction

The mammalian eye is an extension of the brain and even though it is but a few centimeters in diameter, the eye contains an enormous array of cellular and non-cellular elements, many of which are not found anywhere else in the body [1]. The cornea is the interface between the eye and the external environment and is the major refractive surface of the eye. The cornea is composed of three cellular layers: epithelium, stroma, and endothelium. The corneal epithelium undergoes continuous regeneration by mitosis of the basal layer of cells which are derived from ectoderm. Most of the mitotic activity of the corneal epithelium occurs at the limbus where stem cells reside and undergo mitosis to repopulate the corneal surface. The stroma forms the middle layer of the cornea and is a collagen matrix that is secreted by keratocytes, which are derived from mesenchyme. Both the corneal epithelial cells and the keratocytes of the stroma possess significant mitotic and regenerative activities. The corneal endothelium is derived from neural crest cells and is but a single cell layer thick. In the rabbit, corneal endothelial cells are able to proliferate and migrate [2]. However, in humans, corneal endothelial cells possess the capacity to proliferate, but are arrested in the G1-phase of the cell cycle and do not appear to divide *in vivo* [3]. Maintenance of proper corneal hydration is crucial for maintaining corneal clarity and is the primary function of the corneal endothelium. Thus, injury to the corneal endothelium can lead to corneal opacity and eventually, blindness. The lens, like the cornea, provides a clear medium for the transmission of light from the external environment to the retina. Injury to the lens, either by trauma or as a part of the aging process, can compromise the transmission of light rays and hamper vision. The mammalian lens grows throughout life, although the

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growth slows as we age. It is noteworthy that in spite of this continuous cell growth and differentiation, spontaneous tumors of the lens (other than experimentally induced neoplasms) have not been described in any species except the cat [4]. The one million ganglion cells in the retina transmit 500 electrical signals per second, which is equivalent to approximately one billion bits of computer information [1]. The retina performs the extraordinary task of capturing photons and transmitting these signals to the visual cortex of the brain where they are translated into visual images. Maintaining homeostasis of these ocular tissues is paramount for preserving vision. Ocular inflammatory processes, especially those that inflict collateral injury to innocent bystander cells of either the corneal endothelium or the retina, can lead to blindness, as neither of these tissues can regenerate.

The anatomical, physiological, and immunological adaptations that limit immune-mediated inflammation in the eye create the condition known as “immune privilege”, which is believed to be essential for maintaining normal vision [5-8]. This review will focus on the unique properties of the cornea that protect it from infectious diseases while reducing the possibility of immune-mediated injury and blindness.

Immune Privilege of Corneal Allografts

The cornea is the most commonly transplanted tissue in humans and enjoys a success rate that is unrivaled by any other form of solid organ transplantation [9-11]. Although in uncomplicated low risk settings, corneal allografts enjoy a 90% first-year survival rate, the long-term survival is significantly lower, and falls to 74% at 5 years and 62% at 10 years, which is comparable to the survival rates for renal, cardiac, and liver transplants [12]. This has led some to question the validity of immune privilege of corneal allografts. However, corneal allografts are normally performed in the absence of HLA matching and without the use of systemic immunosuppressive drugs; two conditions that would certainly elevate the risk if not guarantee the rejection of renal, cardiac, and liver allografts. Moreover, experiments in both the rat and mouse models of corneal transplantation have confirmed and defined the degree of immune privilege of corneal allografts. That is, in both the rat and mouse, skin allografts mismatched with the recipients at the entire MHC plus multiple minor histocompatibility loci are rejected virtually 100% of the time, while corneal allografts enjoy long-term survival in 50% of the recipients [11, 13]. The immune privilege of corneal allografts mismatched with the recipients only at MHC class I loci or at MHC class II loci is even more impressive, with rejection occurring in 35% and <10% of the hosts respectively [11, 13].

Effect of Blood and Lymphatic Vessels in Maintaining the Immune Privilege of Corneal Allografts

Historically, it was suggested that corneal allografts were devoid of histocompatibility antigens that could provoke immune rejection. However, subsequent studies have clearly shown that MHC class I molecules are expressed on all three layers of the cornea, although the density of these molecules is extraordinarily low on the corneal endothelium [9, 10, 14, 15]. By contrast, MHC class II molecules are not constitutively expressed on any cells within the cornea [9, 10, 14, 15]. The cornea expresses multiple minor histocompatibility molecules including the male-specific H-Y antigen [13, 16-18]. It has been reported that MHC matching does not reduce the incidence of corneal allograft rejection in patients [19]. However, these findings have been disputed and evidence has emerged suggesting that HLA matching is beneficial for patients undergoing penetrating keratoplasty [20-22]. Interestingly, studies in the mouse model of keratoplasty have found that mismatching at minor histocompatibility loci represented the greatest barrier to corneal allograft survival [13]. Thus, in spite of their limited expression of MHC class I and II molecules, corneal

allografts are vulnerable to robust alloimmune responses directed against a myriad of minor histocompatibility antigens.

Under non-pathological conditions, the cornea is one of the few avascular tissues in the body. However, mild trauma or infections of the ocular surface can induce corneal neovascularization. It has long been recognized that corneal allografts transplanted into vascularized graft beds in rodents and rabbits are invariably rejected. The incidence and tempo of corneal allograft rejection soars in murine hosts whose graft beds are prevascularized and contain lymphatic vessels [23]. The absence of lymphatic vessels in particular is important for maintaining immune privilege of corneal allografts, as it prevents the migration of resident antigen presenting cells to the regional lymph nodes where alloimmune responses are generated. Moreover, removal of draining lymph nodes prior to corneal transplantation prevents the rejection of corneal allografts in mice [24]. Blood vessels and lymphatic vessels both respond to VEGF-C and VEGF-D, and can be induced to penetrate the cornea in the mouse [25, 26]. Soluble VEGF receptor-3 can suppress both lymph-angiogenesis and heme-angiogenesis [27]. Recently, Albuquerque and co-workers reported that another VEGF receptor in the form of soluble monomeric VEGFR-2 was a selective antagonist of lymphatic vessel growth and that administration of this soluble receptor inhibited lymphatic vessel formation and doubled corneal allograft survival in mice [28]. It is noteworthy that one of the most potent stimuli for inducing lymphangiogenesis, VEGF-C, is also a strong chemoattractant for corneal dendritic cells (DC), which express VEGFR-3, which is the receptor for VEGF-C [23]. This is noteworthy, as corneal DC are crucial antigen presenting cells for inducing alloimmune responses and initiating corneal allograft rejection in mice [18, 29-31]. *In vivo* treatment with VEGFR-3/Ig blocks DC migration from the corneal allograft bed to regional lymph nodes and produces a dramatic reduction in corneal allograft rejection in mice [23].

Thus, the time-honored observation that the presence of blood vessels in a corneal allograft bed increases the risk for rejection is still valid. However, it is not the presence of blood vessels itself that promotes immune rejection. Instead, the stimuli that induce blood vessel growth (e.g., VEGF-C) also induce the ingrowth of lymphatic vessels and the infiltration of antigen presenting DC, both of which conspire to induce robust alloimmune responses and ultimately, graft rejection.

Immune Deviation and Corneal Allograft Survival

It was reported over 30 years ago that allogeneic cells injected into the anterior chamber (AC) of the mouse and rat eye elicited a unique spectrum of systemic immune responses that was characterized by the antigen-specific suppression of delayed-type hypersensitivity (DTH) and the coincidental deviation of the antibody response from complement-fixing isotypes to non-complement fixing antibody isotypes (e.g., IgG1 in the mouse) [6, 7, 32, 33]. This unique form of immune regulation was termed anterior chamber-associated immune deviation (ACAID) and is believed to contribute to immune privilege in the eye and promote corneal allograft survival [6, 7, 32-34]. Orthotopic corneal allografts lie over the anterior chamber and are in direct contact with the aqueous humor, which contains a myriad of immunosuppressive and anti-inflammatory molecules [35]. Since orthotopic corneal allografts are in direct juxtaposition to the AC, corneal endothelial cells sloughed from the corneal allograft during or after transplantation would be tantamount to an AC injection of allogeneic cells and would be expected to induce ACAID. Mice with long-term surviving corneal allografts display features of ACAID including the antigen-specific down-regulation of DTH responses to the alloantigens expressed on the orthotopic corneal allografts [36]. Moreover, maneuvers that are known to prevent the induction of ACAID also rob the corneal allograft of its immune privilege and promote corneal allograft rejection [34]. That is, the incidence and tempo of corneal allograft rejection rises sharply in mice treated with:

a) splenectomy [37-39]; b) depletion of iNKT cells [40]; c) *in vivo* treatment with anti-IL-10 (Niederkorn unpublished); or d) *in vivo* treatment with low-dose cyclophosphamide that is known to disable T regulatory cells without affecting alloimmune effector responses [41, 42] [Niederkorn, unpublished]. By the same token, induction of ACAID with AC injection of allogeneic cells promotes corneal allograft survival in both the rat [43, 44] and mouse [37].

Efferent Blockade of the Alloimmune Response: Sometimes the Best Defense is a Good Offense

One of the earliest explanations for the immune privilege of corneal allografts proposed that the absence of blood vessels in the corneal graft bed prevented the emigration of immune elements such as alloantibody and lymphocytes from the circulation into the graft. However, this explanation has been thoroughly disproven numerous times in experimental models. For example, mice preimmunized with skin grafts from the same donors who provided subsequent corneal allografts promptly reject corneal allografts placed into avascular graft beds. Nonetheless, there is some merit to the notion that the efferent arm of the alloimmune response is subverted against corneal allografts. Corneal epithelial and endothelial cells are decorated with an interesting array of cell membrane-bound molecules that fend off immunological attack. FasL (CD95L) is expressed on all three layers of the cornea, in the iris, ciliary body, and the retinal pigmented epithelium [45]. FasL induces apoptosis of infiltrating neutrophils and lymphocytes that express its receptor (Fas; CD95) [46]. Two separate studies have demonstrated that the expression of FasL protects the corneal allograft from immune rejection [47, 48]. The eye also expresses other apoptosis-inducing ligands including tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [49, 50] and programmed death ligand-1 (PD-L1) [51, 52]. TRAIL is found in the iris, retinal pigmented epithelium, and all three layers of the cornea [49]. PD-L1 is expressed on corneal epithelial and stromal cells, iris-ciliary body cells, and neural retina in mice and humans [51-53]. Like FasL, engagement of TRAIL-bearing or PD-L1-bearing corneal cells with inflammatory cells expressing their respective receptors results in apoptosis of the latter cells. Although it is not known if TRAIL promotes corneal allograft survival, it is clear that PD-L1 expression is vital for preventing corneal allograft rejection [51, 52]. When PD-L1 on corneal cells engages its receptor, PD-1, on T lymphocytes, it inhibits T lymphocyte proliferation, induces T lymphocyte apoptosis, and prevents T lymphocyte production of the proinflammatory cytokine interferon-γ (IFN-γ). Corneal allografts from PD-L1$^{-/-}$ donors have twice the incidence of immune rejection as corneal allografts that express functional PD-L1 [51, 52]. *In vivo* administration of anti-PD-L1 antibody blocks PD-L1/PD-1 interactions and produces a similar spike in corneal allograft rejection. Thus, corneal allografts have the capacity to repel immunological attack and to a degree, determine their own fate.

The role of antibody in corneal allograft rejection in humans is controversial [54]. Although there is evidence that under certain circumstances alloantibodies can produce corneal allograft rejection in mice [55, 56], the capacity of complement-fixing alloantibodies to mediate corneal allograft rejection is limited by the extensive expression of cell membrane-bound complement regulatory proteins (CRP) that are expressed on corneal cells [57, 58] and soluble CRP that are present in the aqueous humor that bathes the corneal endothelium [57-59]. Corneal endothelial cells do not express cell membrane-bound CRP and are highly susceptible to cytolysis by complement-fixing alloantibodies, which can be demonstrated *in vitro* [55, 60]. However, addition of aqueous humor, which contains soluble CRP, protects corneal endothelial cells from complement-mediated cytolysis [55, 60]. Thus, both cell membrane-bound and soluble forms of CRP shield the corneal allograft from complement-fixing alloantibody and provide a layer of immune privilege that disables the humoral immune response at the graft/host interface.

The low expression of MHC class Ia molecules on the murine corneal endothelium makes it a potentially attractive target for cytolysis by natural killer (NK) cells, which are programmed to lyse MHC class I negative cells [61]. Moreover, it is widely acknowledged that the corneal endothelium is the primary target in the immune rejection of corneal allografts [54] and murine corneal endothelial cells are susceptible to NK cell-mediated cytolysis *in vitro* [62]. Studies in a rat model of penetrating keratoplasty lend support to this hypothesis and have reported a 10-fold increase in the number of NK cells in the aqueous humor compared to the draining lymph nodes in rats undergoing corneal allograft rejection [63]. Although it is possible that under certain circumstances NK cells contribute to corneal allograft rejection, a number of factors might blunt the impact of NK cell-mediated activity directed at the endothelium of the corneal allograft. For example, the aqueous humor that bathes the corneal endothelium contains macrophage migration inhibitory factor (MIF) and transforming growth factor-β (TGF-β), which are potent inhibitors of NK cell-mediated cytolysis [62, 64-66]. MIF produces immediate inhibition of NK cell-mediated cytolysis, while TGF-β displays a similar degree of inhibition, but is delayed until 18 hr after exposure to NK cells. Moreover, human corneal endothelial cells express HLA-G, a nonclassical MHC class I molecule that is a potent inhibitor of NK cell-mediated cytolysis, which may protect human corneal allografts from NK cell-mediated attack [67-70].

Thus, orthotopic corneal allografts are the beneficiaries of the immune privilege that blocks the expression of both the innate and adaptive immune responses, by either disabling or eliminating the effector elements at the graft/host interface.

Infections of the Ocular Surface: Balancing Immune Privilege and Immune Resistance

Immune privilege at the ocular surface and in the anterior chamber of the eye is the product of multiple anatomical, physiological, and immunoregulatory processes that inhibit many innate and adaptive immune responses. The immunological “blind spots” created by immune privilege would seemingly put the eye at risk for infections. Indeed, the ocular surface is exposed to a variety of bacterial, fungal, protozoal, and viral infections, some of which lead to blindness. Ironically, the blindness produced by some ocular surface infections is not due to the crippling effects of immune privilege in combating the infectious agents; instead, the pathological effects are the result of the abrogation of immune privilege and the emergence of an unbridled immune response that in its zeal to attack the ocular pathogen, inflicts significant collateral damage to innocent bystander cells in the eye. Indeed, three of the leading causes of infectious blindness – trachoma, onchocerciasis, and herpes simplex virus (HSV) stromal keratitis – are immune-mediated diseases. Over two decades ago Streilein proposed that the eye and the immune system were engaged in a “dangerous compromise” in which the suppression of some immune responses placed the eye at risk for potentially life-threatening infections [71]. However, this compromise can be breached and immune privilege abrogated if an infection is perceived by the immune system as life-threatening. That is, immune privilege is abolished and robust conventional immune-mediated inflammation is elicited if microbial infections trigger “danger signals” in the form of pro-inflammatory cytokines or if Toll-like receptors (TLR) are engaged. In such conditions, the immune system “decides” that preservation of life supersedes preservation of vision.

Herpes Simples Virus Keratitis

HSV stromal keratitis is the most common cause of infectious blindness in North America [72]. In the United States, approximately 400,000 persons are affected by HSV keratitis, with 20,000 new cases occurring annually. Results from animal studies strongly implicate an

over zealous immune response as the principle cause of blindness associated with HSV stromal keratitis [73]. Both the innate and adaptive immune responses appear to contribute to the pathogenic cascade of HSV stromal keratitis. Many viruses, including HSV, display ligand activity for TLR [74, 75]. TLR are the sensing elements of the innate immune system and are a type of pattern recognition receptor (PRR) that recognizes molecules that are expressed by a wide array of pathogens, such as HSV. Once engaged, TLR activate cytokine genes that set into motion a complex inflammatory cascade. Early events in the pathogenesis of HSV keratitis involve the production of multiple cytokines including IL-1β, IL-6, and TNF-α, whose production can be significantly affected by engagement of TLR2 [72]. That is, production of these cytokines and the severity of HSV keratitis are greatly reduced in TLR2 $^{-/-}$ mice [76]. Cellular elements of the innate immune response, namely natural killer (NK) cells, participate in the pathogenesis of HSV stromal keratitis through their elaboration of cytokines and chemokines that attract and activate neutrophils, which are the end-stage effector cells in HSV stromal keratitis in the mouse [77-81].

The adaptive immune system is also intimately involved in the pathophysiology of HSV stromal keratitis [73]. $CD4^+$ T cells in particular appear to play a crucial role in HSV stromal keratitis. The severity of HSV stromal keratitis is correlated with the intensity of DTH responses to HSV-1 antigens and the density of corneal antigen-presenting Langerhans cells (LC) [82-85]. The absence of MHC class II positive LC in the central corneal epithelum plays an important role in reducing the immunogenicity of corneal allografts and in supporting immune privilege of the ocular surface [11, 14, 15, 30, 54]. Corneal LC are crucial for the induction of HSV-specific $CD4^+$ T cell responses and the generation of corneal lesions in HSV stromal keratitis [84]. Corneal lesions are exacerbated in eyes pretreated with local injection of the cytokine IL-1, which induces centripetal migration of LC into the central corneal epithelium prior to exposure to topical infections with HSV-1 [84]. However, inactivating LC by exposing the cornea to ultraviolet irradiation immediately prior to topical exposure to HSV-1 dramatically reduces the generation of HSV-specific DTH and mitigates the severity of HSV stromal keratitis [84]. Likewise, maneuvers that lead to the generation of HSV-specific T regulatory cells, such as injecting HSV-1 into the AC prior to topical infection, mitigate HSV keratitis, down-regulate DTH responses to HSV antigens and produce a commensurate reduction in the severity of HSV keratitis [86]. Topical application of the immunosuppressive cytokine IL-10 or *in situ* transfer of IL-10 cDNA into corneal cells also inhibits the induction of HSV-specific DTH and mitigates HSV stromal keratitis [87, 88]. Thus, dampening, but not completely disarming the immune response to HSV antigens, protects the eye and preserves vision. However, complete inhibition of viral immunity poses a serious risk to the survival of the host. T cell-deficient nude mice cannot mount adaptive immune responses and in a sense, represent an extreme form of immune privilege. Nude mice do not develop HSV keratitis, which supports the notion that the pathogenesis of this disease is mediated by the adaptive immune response to HSV antigens [89]. However, the preservation of vision comes at a high price, as nude mice infected by topical application of HSV-1 die from viral encephalitis [89]. In the case of nude mice, the “immune privilege” is immutable and the consequences are lethal. This underscores the importance of allowing ocular immune privilege to be abrogated in conditions in which the infectious agent is life-threatening. Under these circumstances violating the compromise between the eye and the immune system is mandatory.

Pseudomonas Keratitis

A common misconception regarding immune privilege is that it is an “all or none” proposition. In some circumstances immune privilege appears to be complete as shown by the >90% acceptance of MHC class II-mismatched corneal allografts compared to the 100% rejection of skin allografts in the same donor-host combinations [9-11, 15]. In other cases,

immune privilege is partial as revealed by the 50% acceptance of corneal allografts mismatched at the entire MHC plus multiple minor histocompatibility loci [9-11, 15]. *Pseudomonas* keratitis provides an interesting example of the plasticity of immune privilege or more precisely, the tenuous nature of ocular immune regulation and the profound impact this can have on the fate of the eye and the preservation of vision. *Pseudomonas aeruginosa* is a Gram-negative bacterium that is a common cause of bacterial keratitis. The pathology and blindness caused by *Pseudomonas* keratitis are largely due to the host's inflammatory response that involves elements of both the innate and adaptive immune responses [90]. Early studies in mice with corneal infections with *P. aeruginosa* revealed that the disease typically follows one of two courses. In Th1 prone hosts, such as the C57BL/6 mouse strain, the corneas perforate within approximately seven days [91]. By contrast, mice favoring Th2 immune responses, such as BALB/c mice, exhibit a milder disease in which the corneas infected with *P. aeruginosa* do not perforate. C57BL/6 mice depleted of $CD4^+$ T cells and infected with *P. aeruginosa* do not perforate, lending further support to the hypothesis that T cell immune responses contribute to the pathophysiology of *Pseudomonas* keratitis [91]. Although IFN-γ is the signature cytokine for $CD4^+$ Th1 cells and thus, might be expected to contribute to corneal perforation in the Th1-prone C57BL/6 mouse, its role in *Pseudomonas* keratitis is much more complicated than simply tilting the immune response to a Th1 pathway and away from a Th2 response. Even though the BALB/c mouse is Th2-prone, IFN-© is crucial for disease resolution in this mouse strain [92]. BALB/c IFN-$\gamma^{-/-}$ mice exhibit a 1-2 log increase in the corneal bacterial cell counts and undergo corneal perforation compared to their wild-type counterparts, who are able to control their bacterial infections and whose corneas do not usually perforate [93]. If T cell-dependent immune responses in the BALB/c mouse are skewed toward a Th2 pathway, what is the source of IFN-γ in *Pseudomonas* keratitis in these mice? Lighvani and co-workers found that IFN-© was produced locally in the infected corneas even though T cells could not be detected in these tissues [92]. Closer examination revealed that NK cells were present in the infected corneas and were an important source of the IFN-©. Further investigation revealed that recognition of *Pseudomonas* endotoxin by antigen-presenting LC in the corneas of infected mice induced the LC to produce IL-12, which in turn stimulated NKT cells to produce IFN-©. The IFN-© produced by NKT cells stimulated NK cells in the cornea to produce additional IFN-©, which was found to be essential for the clearance of the bacteria and the prevention of corneal perforation [94]. The cascade-like production of IFN-© by both NKT and NK cells is necessary for the activation of neutrophils and the clearance of bacteria. The failure to activate neutrophils results in the accumulation of bacteria, which culminates in corneal perforation. Thus, the innate and adaptive immune responses must be carefully choreographed for the clearance of *Pseudomonas* infections of the cornea. The adaptive immune response is needed for the activation of innate effector elements, namely neutrophils. Although an overactive $CD4^+$ T cell response can promote bacterial clearance, it does so at the cost of immune-mediated perforation of the cornea. This delicate balance in the innate and adaptive immune responses underscores the importance of immune regulation in protecting the eye from infectious agents while guarding against inflicting irreparable injury to the cornea and blindness.

Dry Eye Disease: A Newly Recognized Autoimmune Disease of the Ocular Surface

Dry eye disease is a complex inflammatory disorder that involves the cornea, conjunctiva, and lacrimal gland, and is estimated to affect over nine million Americans [95-98]. In its most severe form, dry eye disease can culminate in corneal ulceration, reduced vision, and in some cases, blindness. A growing body of evidence suggests that dry eye disease is an inflammatory disorder of the lacrimal functional unit (LFU; cornea, conjunctiva, lacrimal

glands, and meibomian glands). Inflammation correlates with elevation of proinflammatory cytokines in the tears and the LFU, increased epithelial cell apoptosis, decreased tear production, and diminished number of goblet cells in the conjunctiva. Although the pathogenesis of dry eye remains poorly understood, it is widely agreed that a common feature is inflammation of the ocular surface and in severe cases, the lacrimal gland. Several findings implicate T cells in the pathogenesis of dry eye disease: a) T cells are found infiltrating the conjunctiva in clinical specimens from patients and experimental animals [99-102]; b) mice with experimental dry eye display a steep increase in the presence of activated T cells in the lymph nodes draining the conjunctiva [103]; c) rats immunized with a lacrimal gland protein, kallikrein 1b22 (Klkb22), develop keratoconjunctivitis and produce T cells that are capable of adoptively transferring lacrimal gland and conjunctival inflammation to naive recipients [100]; d) adoptive transfer of $CD4^+$ T cells from mice with experimental dry eye disease to T cell-deficient mice produces keratoconjunctivitis [101]; and e) topical administration of the T cell immunosuppressive agent, cyclosporine, ameliorates the symptoms of dry disease in some patients [98, 104].

Mouse models suggest that both Th1 and Th17 cells contribute to the pathogenesis of dry eye disease [99, 103, 105, 106]. Mice with experimental dry eye disease have increased numbers of $CD4^+$ IFN-γ^+ T cells infiltrating their conjunctiva and elevated levels of IFN-γ in their tears, which are not observed in similarly treated IFN-$\gamma^{-/-}$ mice [99]. Using the same model of dry eye disease, El Annan *et al.* detected a >100% increase in the number of IFN-γ-expressing T cells in the draining cervical lymph nodes of dry eye mice [103]. Recent evidence suggests that Th17 cells contribute to the pathogenesis of dry eye disease [106, 107]. Conjunctivae from dry eye patients express significantly elevated levels of IL-17A transcripts [106]. Mice with experimental dry eye disease display increased transcript and protein expression of IL-17A and Th17-associated genes IL-6, IL-23 and TGF-β in conjunctival and corneal tissues [106]. Moreover, *in vivo* neutralization of IL-17 produces significant amelioration of corneal epithelial dysfunction in mice with dry eye disease [105, 106].

Results from animal studies suggest that T regulatory cells (T_{regs}) have an important impact on the pathogenesis of dry eye disease [101, 105]. Wild-type mice subjected to desiccating stress (DS) develop a mild form of dry eye disease. However, $CD4^+$ T cells collected from these mice produce severe dry eye disease when adoptively transferred to athymic, T cell-deficient nude mice, even if the nude mice are not subjected to DS [101]. The hypothesis that the severe form of dry eye disease in T cell-deficient nude mice is due to their absence of T_{regs} is supported by the observation that wild-type mice treated with anti-CD25 antibody to disable T_{regs} develop full-blown dry eye disease if these mice are subsequently subjected to DS [101]. Moreover, analysis of the T cell population in draining cervical lymph nodes from mice with dry eye disease reveals that the $CD4^+CD25^+$ $Foxp3^+$ putative T_{regs} display a significantly reduced capacity to suppress Th17 cell proliferation *in vitro* [107]. Although much remains to be learned about the pathogenesis of dry eye disease, the weight of evidence suggests that it represents a breakdown in ocular immune privilege. Successful re-establishment of immune privilege and restoration of homeostasis of the ocular immune response should pay big dividends in the management of this debilitating disease.

Conclusions

The statement that “the cornea is the window to the eye and to ocular immunity” is true, both literally and metaphorically. Regulating ocular inflammation is crucial for preserving the clarity of the eye's window. The corneal endothelium is but a single cell layer thick and composed of only 400,000 cells, which are amitotic [108]. Injury to the corneal endothelium compromises the ionic pumping function of the cornea and results in corneal opacity. Thus,

a single layer of amitotic corneal endothelial cells stands between crisp vision and blindness. The cornea and the underlying anterior chamber possess unique attributes that protect the cornea and the eye from immune-mediated inflammation that can rob the cornea of its clarity. The unique spectrum of immunological adaptations is termed “immune privilege” and is believed to be essential for the preservation of vision. The cornea is not only a physical “window”, but is also a metaphorical “window” that has allowed investigators to make important discoveries in mainstream immunology. Among these are: a) the role of LC in provoking HSV keratitis and corneal allograft rejection; b) the role of FasL in maintaining immune privilege and promoting corneal allograft survival; c) the collaboration between soluble CRP in the aqueous humor that bathes the corneal endothelium and the cell membrane-bound CRP that shield the ocular surface from complement-mediated injury and the proinflammatory effects of complement components C3a and C5a; and e) the orchestration of innate and adaptive immune responses in controlling bacterial keratitis without inflicting immune-mediated injury to the “eye's window”.

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