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Chapter 99

Ocular Mucosal Immunity

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Chapter Outline

The innate and adaptive immune systems contribute to ocular immunity by minimizing damage to ocular tissues and preventing microbial invasion. The mucosal immune system defends the ocular surface against antigenic challenge (Franklin, 1989; McClellan, 1997; Montgomery et al., 1994; Montgomery and Whittum-Hudson, 1996; Sack et al., 2001; Sullivan, 1999). This immunologic role is mediated primarily through secretory immunoglobulin A (S-IgA) antibodies, which are known to inhibit viral adhesion and internalization; prevent bacterial attachment, colonization, and activity; interfere with parasitic infestation; and reduce antigen-related damage in mucosal sites (Childers et al., 1989; Mestecky and McGhee, 1987; Ogra et al., 1999; Underdown and Schiff, 1986). Thus, the ocular mucosal immune system protects the eye against allergic, inflammatory, and infectious disease, thereby promoting conjunctival and corneal integrity and preserving visual acuity. This chapter reviews the immunologic architecture and regulation of the ocular mucosal immune system and explores the effect of ocular infection and autoimmune disease on this system's structure and function. For information on nonmucosal aspects of ocular immunity, such as anterior chamber-associated immune deviation and retinal immunology, the reader may refer to several excellent sources (Ksander and Streilein, 1994; Pepose et al., 1996; Streilein et al., 2002; Caspi, 2010).

ARCHITECTURE OF OCULAR MUCOSAL DEFENSES

The epithelia of the conjunctiva, along with the lacrimal drainage system, the tear film, the lacrimal glands, and the eyelids, act as a functional unit to preserve the quality of the refractive surface of the cornea for the maintenance of visual function. For the purpose of defense, the cornea depends on its major support tissue, the conjunctiva, in addition to soluble factors provided by the lacrimal glands via the tear film. These components are in anatomic continuity and share feedback mechanisms by which simultaneous reactions occur in response to a single stimulus (Rolando and Zierhut, 2001; Knop and Knop, 2002a, 2002b, 2005a, 2007).

Lacrimal Gland

The principal tissues involved in immunologic protection of the ocular surface are the lacrimal gland and the conjunctiva. The lacrimal gland, which serves as the predominant source of tear S-IgA antibodies, is an effector tissue of the eye's mucosal immune defense (Franklin, 1989; McClellan, 1997; Montgomery and Whittum-Hudson, 1996; Peppard and Montgomery, 1990; Sullivan, 1999; Sullivan and Allansmith, 1984). Until recently it was considered as the only source of IgA present in the tear film (Sacks et al., 1986; Sullivan, 1999). The lacrimal gland is made up of acinar units consisting of secretory acinar epithelial cells, which are surrounded by myoepithelial cells and a basement membrane. The acinar units are interconnected by ductules, which drain into the glandular ducts and from there to the superotemporal conjunctival cul-de-sac via 10–12 lacrimal excretory ducts (Figure 1; Wieczorek et al., 1988). Between the acinar units is a loose connective tissue resembling that of the conjunctiva and continuous with it along the excretory ducts (Knop and Knop, 2007). Smaller accessory lacrimal glands are also found in the upper and lower conjunctiva, which drain directly through the epithelium (Figure 2; Sacks et al., 1986).

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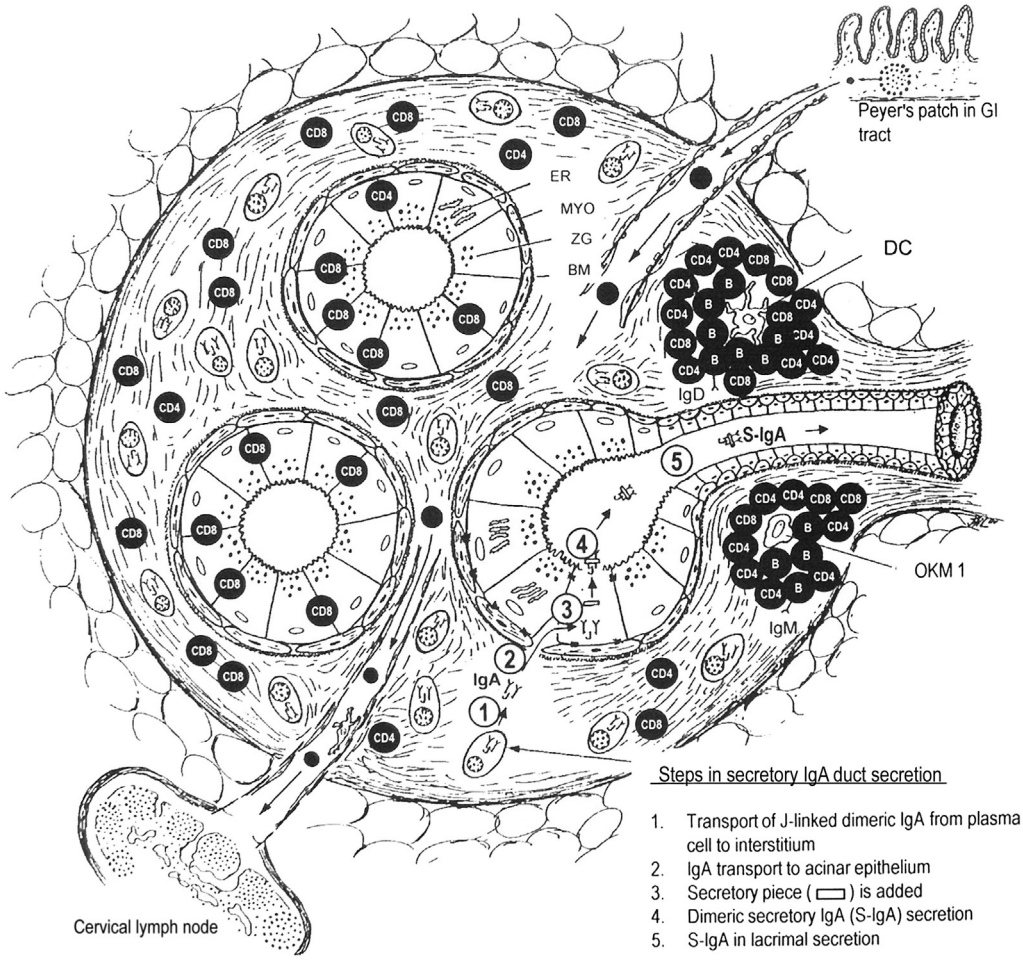

FIGURE 1 Schematic representation of the secretory immune system of the human lacrimal gland. Topographical features include acinar cells having endoplasmic reticulum and lysozyme- and lactoferrin-positive zymogen granules, where secretory component (SC) is synthesized and secreted; myoepithelial cells, which are adjacent to acinar cells and are surrounded by a basement membrane; interstitial plasma cells, which are the primary lymphoid cell and produce principally IgA, but also some IgG, IgM or IgD; $CD4^+$ cells, consisting of T helper and regulatory (Treg) subsets, and $CD8^+$ cells, which include T effector and Treg subsets and natural killer cells distributed throughout the interstitium, the intercellular spaces between acinar or ductal cells, and in periductular lymphoid aggregates; B cells; Langerhans'-type dendritic cells and $OKM1^+$ monocyte-macrophages located predominantly in periductular lymphoid aggregates, which most often appear as primary follicles without germinal center formation and may be active in antigen processing; and unlabeled, darkened cells, which refer to circulating T or B lymphocytes, which may originate in other mucosal tissues (e.g., intestinal Peyer's patch) and, if not retained locally, possibly exit the lacrimal gland through lymphatic channels to regional CLNs or preauricular lymph nodes. Steps in S-IgA production include (1) transport of J-linked dIgA from plasma cells to the interstitium, (2) IgA transport to the acinar epithelium, (3) secretory piece added, (4) dimeric S-IgA secretion, and (5) S-IgA in lacrimal secretion. ER, endoplasmic reticulum; ZG, zymogen granules; MYO, myoepithelial cells; BM, basement membrane; DC, dendritic cell; GI, gastrointestinal; B, B cell; CLN, cervical lymph node. *This figure has been modified and published courtesy of Ophthalmology 1988; 95, 100–109.*

Lacrimal glands contain a diverse array of leukocytes, including plasma cells; T and B lymphocytes bearing the human mucosal lymphocyte-1 antigen (beta 7-integrin); and dendritic cells, macrophages, monocytes, and natural killer cells (Table 1; Figure 1). In humans, plasma cells represent more than 50% of all mononuclear cells in lacrimal tissue, most being immunoglobulin (Ig)-A-positive with IgA1 and IgA2 expressed. A high percentage of lacrimal IgA plasma cells synthesize J chain and produce polymeric IgA (pIgA). The pIgA binds the polyimmunoglobulin receptor (membrane insert piece + secretory component (SC)) produced by epithelial cells, undergoes transcytosis, and is released as S-IgA, the major effector molecule in mucosal defense (Allansmith et al., 1985; Allansmith and Gillette, 1980; Brandtzaeg, 1985; Childers et al., 1989; Crago et al., 1984; Franklin et al., 1973; Gillette et al., 1980; Kett et al., 1986; Mestecky and McGhee, 1987; Underdown and Schiff, 1986; Wieczorek et al., 1988). These cells are complemented by limited numbers of IgG, IgM, IgE, and IgD plasma cells (Allansmith et al., 1976b; Brandtzaeg et al., 1979, 1987).

The second most frequent lymphocyte population in human lacrimal tissue consists of T cells situated between

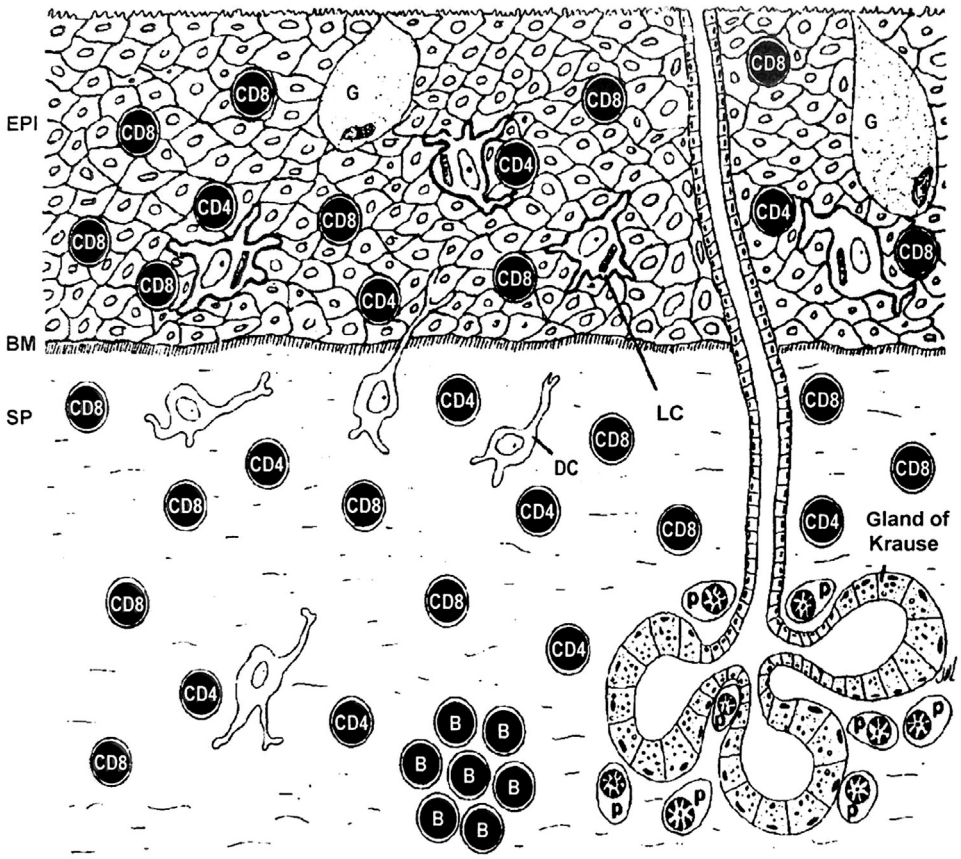

FIGURE 2 Diagrammatic representation of lymphocyte populations in the normal human conjunctiva. The EPI contains CD4 and CD8 T cells consisting of various helper, regulatory, and effector subsets as well as Langerhans-type dendritic cells. The substantia propria also contains these T cell populations, as well as non-Langerhans interdigitating dendritic cells and lymphoid aggregates harboring predominately B cells. The accessory lacrimal gland (gland of Krause) is analogous to the main lacrimal gland and contains several plasma cells. G, intraepithelial mucus-producing goblet cells. EPI, epithelium; LC, Langerhans-type dendritic cells; SP, substantia propria; DC, dendritic cells; B, B cells; P, plasma cells. *This figure has been modified and published courtesy of Ophthalmology 1986; 93, 1276–1283.*

acinar and ductal epithelial cells, throughout glandular interstitial regions, and within small, periductular, lymphoid aggregates. Ordinary lymphoid follicles are rarely observed. The distribution of T cells varies topographically by subclass with $CD8^+$ cells generally more frequent than $CD4^+$ cells (Wieczorek et al., 1988). $CD4^+$ regulatory T cells (Treg) patrol the lacrimal glands and play a role in protecting against autoimmunity (Ishimaru et al., 2010). Minor populations of lacrimal immunocytes include surface Ig-bearing B cells; Langerhans-type dendritic cells; monocyte-macrophages; and activated, interleukin (IL)-2 positive, T cells, which occur almost exclusively in periductular foci, appearing as primary follicles without germinal centers (Gudmundsson et al., 1988; Wieczorek et al., 1988; Dua et al., 1994; Pepose et al., 1996). Lacrimal glands of rats, rabbits, and mice share many of the immune features of the human gland (Schechter et al., 2010; see Table 1).

In addition to S-IgA, the lacrimal gland supplies several nonspecific factors to the aqueous layer of the tear film that contribute to the mucosal defense of the outer eye. Lacrimal acinar cells produce lysozyme and lactoferrin, which have antibacterial properties. Lysozyme is a bacteriolytic enzyme that makes up 40% of tear proteins (Gillette and Allansmith, 1980; Gillette et al., 1981). Lactoferrin makes up 25% of the protein in human tears. Lacrimal glands also produce and secrete into the tears antimicrobial peptides, including defensins (Haynes et al., 1998; McDermott, 2004). Many additional molecules including growth factors and cytokines related to ocular surface health are produced in the lacrimal gland and have been identified in tears (Sack et al., 2005). The immunologic characteristics of human accessory lacrimal tissue appear to be identical to those of the major lacrimal gland (Gillette et al., 1980, 1981; Sacks et al., 1986).

The migration of lymphocytes into the lacrimal gland appears to be random (McGee and Franklin, 1984). However, the selective retention and heterogeneous distribution of IgA-containing or T cells within lacrimal tissue are not random and may be stimulated by antigenic challenge and regulated by microenvironmental, endocrine, neural,

TABLE 1 Lymphocyte Populations Identified in Lacrimal Glands of Various Species

Species	References
Human	
• IgA (predominant; both IgA1 and IgA2), IgG, IgM, IgD, and IgE plasma cells • $CD8^+$ (predominant), $CD4^+$, and activated ($IL\text{-}2^+$) T cells • Surface IgM- (predominant), IgD-, IgG-, or IgA-bearing B cells • HML-1^+ ($\alpha E\beta 7$) lymphocytes • Macrophages, monocytes, and dendritic cells	Franklin et al. (1973), Allansmith et al. (1976a, 1985), Brandtzaeg et al. (1979, 1987), Gillette et al. (1980), Crago et al. (1984), Wieczorek et al. (1988), Dua et al. (1994), Fujihara et al. (1999), Schechter et al. (2010), and Brandtzaeg (1985)
Rabbit	
• IgA (predominant) and IgG plasma cells • Mast cells	Shimada and Silverstein (1975), Franklin et al. (1979), Jackson and Mestecky (1981), and Schechter et al. (2010)
Rat	
• IgA (predominant), IgG (IgG1, IgG2a, IgG2b, IgG2c) and IgM plasma cells • Surface IgM-, IgA-, and IgG-bearing B cells • Macrophages, mast cells • Recent thymic emigrants; $CD8^+$ and $CD4^+$, effector, naïve and memory (rare) T cells; $\alpha E\beta 7^+$ T cells; natural killer T cells; and possibly extrathymic T cells • Mast cells	Ebersole et al. (1988), Gudmundsson et al. (1985), Allansmith et al. (1987), Hann et al. (1988), Pappo et al. (1988), Montgomery et al. (1990), Sullivan et al. (1990c, 2005), Williams et al. (1994), O'Sullivan et al. (1998, 2001), Sullivan et al. (1998), and Schechter et al. (2010)
Mouse	
• IgA (predominant), IgG, and IgM plasma cells • Surface IgA-, IgG-, or IgM-bearing B cells • Natural killer T cells, B1 cells • Mast cells • Th17, Treg	McGee and Franklin (1984), Montgomery et al. (1985), Saitoh-Inagawa et al. (2000), Chauhan et al. (2009), and Schechter et al. (2010)

Ig, immunoglobulin; Treg, regulatory T cell; HML-1, human mucosal lymphocyte-1 antigen.

T cell, and/or acinar epithelial cell signals (Jackson and Mestecky, 1981; Franklin et al., 1985, 1988; Walcott et al., 1986; Allansmith et al., 1987; Hann et al., 1988; Franklin, 1989; Franklin and Shephard, 1990; Sullivan et al., 1990a, 1998). The lymphocytic accumulation in, or adherence to, lacrimal tissue appears to require receptors; divalent cations; intact metabolic, oxidative phosphorylation; and contractile microfilament systems. It also depends on cellular surface protein and carbohydrate determinants (O'Sullivan and Montgomery, 1990; O'Sullivan et al., 1994a,b, 1995).

Conjunctiva and Lacrimal Drainage System

The conjunctival tissue consists of an outer stratified, nonsquamous epithelium consisting of two to three layers and having mainly cuboidal morphology with interspersed goblet cells, a basement membrane, and underlying loose connective tissue known as the lamina propria. The lamina propria contains bone marrow-derived cells that form a mucosal immune system known as conjunctival-associated lymphoid tissue (CALT), a normal, noninflammatory component of the human ocular surface that contributes in the production of immune mediators as well as regulation of the local immune response (Chandler and Gillette, 1983; Kraehenbuhl and Neutra, 1992; Dua et al., 1994; Knop et al., 2008; Knop and Knop, 2005a, 2007; Steven and Gebert, 2009). The overlying epithelium is also endowed with intraepithelial lymphocytes (IELs), which balance IEL-mediated production of inflammatory mediators and actively generated immune tolerance. Flow cytometric analyses showed higher percentages of $CD3^+$ and $CD8^+$ IELs in the upper bulbar and tarsal conjunctiva than in the inferior tarsal-bulbar-fornix, where $CD19^+$ B cells were increased (Reinoso et al., 2012). Figure 2 (modified from Sacks et al. (1986)) diagrams the major features of the human conjunctiva.

In some animal species, components of CALT were described in conjunctiva, showing species-specific differences (Axelrod and Chandler, 1979; Franklin and Remus, 1984; Latkovic, 1989; Ruskell, 1995; Knop and Knop, 1996; Chodosh et al., 1998a,b; Chodosh and Kennedy, 2002). Human studies using histochemical methods (Kessing, 1968; Allansmith et al., 1978) and immunohistochemical studies analyzing small biopsy specimens (Sacks et al., 1986; Dua et al., 1994; Hingorani et al., 1997) historically reported

differing results as to the number and localization of the cells and did not clearly establish whether conjunctival lymphoid cells formed a functionally active CALT system. Knop and Knop (2000) analyzed whole mounts of normal human conjunctival sacs and determined that the associated lymphoid tissue contains all of the components necessary for an immune response and that expression of IgA and SC indicates that the conjunctiva belongs to the mucosal immune system. Lymphoid tissue was mainly observed in the palpebral conjunctiva, more pronounced in the upper lid than the lower. Diffuse lymphoid tissue of lymphocytes (predominantly T cells) and plasma cells (most of which were IgA^+) formed a thin layer in the lamina propria of all of the conjunctival sacs. The overlying epithelium produced SC. In three fifths of the specimens, organized follicular accumulations having a lenticular shape, composed of B lymphocytes, and covered by a lymphoepithelium were embedded in the diffuse lymphoid layer. High endothelial venules were present in all types of lymphoid tissue (Knop and Knop, 1996, 2000, 2001). Unlike the M cell-containing follicle-associated epithelium (FAE) covering Peyer's patches, no differences between the appearance of the microvilli of conjunctival FAE and that of non-follicle-associated epithelium were noted by transmission electron microscopy in 13 mammalian species (Chodosh et al., 1998b; Chodosh and Kennedy, 2002). Using ultrastructural methods, other investigators were able to demonstrate M cells in the CALT of rabbits (Knop and Knop, 2005b). Despite the apparent ubiquity of conjunctival lymphoid follicles in rabbits, ferrets, guinea pigs, cats, dogs, pigs, sheep, cows, rhesus monkeys, baboons, owl monkeys, bush baby monkeys, and humans, few or no lymphoid tissues were identified in mice or rats (Setzer et al., 1987; Chodosh et al., 1998b). CALT was reported on the nictitating membrane of only 1 of 18 eyes of untreated BALB/c mice, although more was seen after ovalbumin treatment (Sakimoto et al., 2002) or after repeated challenge with *Chlamydia trachomatis* serovar C or a solution of ovalbumin and cholera toxin B (Steven et al., 2008), indicating that although CALT is not present in normal mouse conjunctiva, it is inducible. Conjunctival lymphoid follicles have recently been reported in the eyes of 7 of 15 New World rodents (Astley et al., 2007). These authors suggest that the deer mouse (*Peromyscus maniculatus*) might serve as a useful model species for studying ocular infections and immunology of the eye. The presence of organized CALT appears to be related to antigenic exposure, as evidenced by the rapid increase in conjunctival lymphoid tissue in early youth, a reduced amount under germfree conditions, and a slow decline with advancing age (Osterlind, 1944; McMaster et al., 1967).

The conjunctiva contains the immunologic capacity for antigen processing, cell-mediated immunity, and hypersensitivity responses (Allansmith et al., 1981; Chandler and Gillette, 1983; Hann et al., 1985; Sacks et al., 1986; Cornell-Bell et al., 1986; Abelson and Smith, 1991; Montgomery and Whittum-Hudson, 1996). Other bone-marrow-derived leukocytes reside in the conjunctiva and act mainly for the innate immune system. An immunohistological study reported $CD68^+$ macrophages as the second most prevalent leukocyte population in the conjunctiva (Hingorani et al., 1997). Dendritic Langerhans cells are regularly found, express activation markers, and function as professional antigen-presenting cells (APCs; Chandler and Gillette, 1983). They are critical regulators of immunity and link innate and adaptive immune effector mechanisms (Banchereau and Steinman, 1998). Mast cells produce factors, including cytokines, which recruit other leukocytes and orchestrate inflammatory reactions to destroy pathogens (Morgan et al., 1991). Granulocytes only emigrate from the blood if recruited (Allansmith et al., 1978; Knop and Knop, 2000). When the topographical distribution of CALT is projected onto the ocular surface, it overlies the cornea during eye closure and is therefore in a suitable position to mediate corneal immune protection during blinking and overnight. The CALT has the capacity to detect corneal antigens and to prime effector cells as well as distributing protective factors such as S-IgA (Knop and Knop, 2005a).

The lacrimal drainage system is continuous with the conjunctiva via the lacrimal puncta and canaliculi. The epithelium is a stratified squamous, nonkeratinized layer inside of the canaliculi and becomes a pseudostratified epithelium with columnar ciliated cells in the lacrimal sac and nasolacrimal duct (Knop and Knop, 2001). The mucosa contains diffuse lymphatic tissue and organized follicles, similar to the lymphoid tissue observed in the conjunctiva. IgA^+ plasma cells and the IgA transporter protein, SC, are demonstrated in the lamina propria and the overlying epithelium, respectively, indicating local production of specific S-IgA. These components contribute to ocular mucosal secretory immunity and have been termed lacrimal drainage-associated lymphoid tissue (LDALT) (Knop and Knop, 2001, 2005a; Paulsen, 2003; Paulsen et al., 2000, 2002, 2003) or tear duct-associated lymphoid tissue (Nagatake et al., 2009). In mouse tear duct-associated lymphoid tissue, postnatal organogenesis is independent of $CD3^-CD4^+CD45^+$ lymphoid tissue inducer cells and signaling through organogenesis regulators responsible for the development of secondary lymphoid tissues such as lymph nodes and Peyer's patches (Nagatake et al., 2009).

CALT and LDALT appear to be regularly present and to belong to the common mucosal immune system and to the secretory immune system. Together with the lacrimal gland, they form an eye-associated lymphoid tissue connected by tear flow, lymphocyte migration, and the neural reflex arc, and they play a major role in preserving ocular surface integrity (Knop and Knop, 2000, 2001, 2005a, 2007; Rolando and Zierhut, 2001).

Cornea

Although the conjunctiva and the cornea are similarly exposed to the outside environment, the defensive mechanisms of the two tissues are fundamentally different. Whereas the conjunctiva is a highly reactive tissue that is protected by a potent immune system, the cornea is relatively unreactive, with the immune system repressed to some extent to avoid inflammatory reactions that could compromise the cornea's transparency. Defense is aided by cell polarity, tight cell junctions, and continual replacement of the epithelium. The epithelium produces very high levels of membrane-bound complement inhibitors and plasminogen activator inhibitor type 2, and it has the ability to produce alpha2-macroglobulin and alpha1-antiproteinase, thereby reducing the risk of autologous cell damage (Sack et al., 2001). The cornea also produces very high levels of antioxidants (Rose et al., 1998) that may protect the ocular surface from reactive oxygen species produced by activated polymorphonuclear (PMN) cells. The cornea possesses interstitial IgA, IgG, IgM, IgD, and IgE, which appear to originate from serum, diffuse from the limbal to central regions, and require extended time periods (e.g., months) for complete turnover (Allansmith and McClellan, 1975; Verhagen et al., 1990; Pleyer et al., 1996). SC is not produced by the "normal" avascular corneal epithelium or stroma (Allansmith and Gillette, 1980). The peripheral cornea, which is in close contact with the conjunctival vasculature, may also contain Langerhans cells and macrophages (Pleyer et al., 1996). Although early studies determined that lymphocytes and differentiated Langerhans cells are essentially absent from the normal central cornea (Allansmith et al., 1978; Seto et al., 1987), subsequent studies using immunohistochemical confocal microscopic analyses of rodent corneal whole mounts have demonstrated the presence of small numbers of $CD3^+$ T cells (both $CD4^+$ and $CD8^+$), macrophages, and dendritic cells (Langerhans cells), but no B cells, in the peripheral cornea and limbus (Yang et al., 1998). In addition to these peripheral cells, a novel major histocompatibility complex (MHC) class II-negative population of resident corneal Langerhans-type dendritic cells has been identified in the central cornea of mice (Hamrah et al., 2002) and humans (Yamagami et al., 2005a,b). The corneal stroma is endowed with at least three bone-marrow-derived dendritic cell subsets (Hamrah et al., 2003) as well as a novel macrophage population (Brissette-Storkus et al., 2002). These dendritic cell subsets demonstrate an interesting stratification within noninflamed murine corneas that suggests a progression from APC function at the exposed surface to an innate immune barrier function deeper in the stroma (Knickelbein et al., 2009). In inflammation, these dendritic cells become activated, as evidenced by expression of B7 co-stimulatory markers, and after corneal transplantation they express MHC class II and migrate to the draining lymph nodes (Liu et al., 2002b; Hamrah et al., 2003). These findings refute the tenet that the cornea is immune privileged because of a lack of resident lymphoreticular cells or because of antigenic sequestration from systemic immunity. Membrane-bound or soluble chemotactic factors, locally produced in the periphery, prevent Langerhans cell migration from the limbus unless a stronger stimulus (e.g., IL-1) is produced. IL-1β is secreted by corneal epithelial cells in response to interferon (IFN)-γ or bacterial infection (Wakefield and Lloyd, 1992). Further, normal keratocytes express MHC class II molecules in response to inflammation, suggesting that keratocytes collaborate with APCs in antigen presentation to T cells, leading to activation of the humoral response, cell-mediated immunity, and inflammation (Niederkorn, 1990). During inflammation, macrophages and neutrophils extravasate from the vasculature and generate cytokines, including transforming growth factor (TGF)-β, IL-1, IL-6, and tumor necrosis factor (TNF)-β, which facilitate T cell and B cell differentiation and activation. Cytokines produced by immune cells and keratocytes exacerbate the inflammatory response, complement-mediated cytotoxicity, and angiogenesis. To counter the cytotoxic damage that may ensue from inflammation, the cornea protects itself by producing TGF-β, which suppresses cell-mediated immune responses, and Fas-L, which prevents cell-mediated damage to the epithelial cells (Sack et al., 2001).

Tear Film

The preocular tear film plays a critical role in the eye's defense against microbial and antigenic exposure as well as in the maintenance of corneal clarity and visual ability (Holly, 1987; Lemp and Marquardt, 1992; Lemp, 1995; Rolando and Zierhut, 2001). These functions are extremely dependent on the stability, tonicity, and composition of the tear film structure, the actual architecture of which is still not totally resolved. The smooth refractive tear film is maintained by the blinking of the eyelid to replenish the tears over the surface of the cornea. Early hypotheses of tear film architecture considered it to have three distinct layers, including an underlying mucin layer adjacent to the epithelial surface; a middle aqueous component; and a thin overlying lipid layer secreted from the conjunctival goblet cells, the lacrimal glands, and the meibomian glands, respectively (Holly, 1987; Whitcher, 1987; Dartt, 1992; Dartt and Sullivan, 2000). More recent models indicate that the mucins are mixed within the aqueous tear fluid, with the mucins having a decreasing gradient of concentration from the epithelium to the surface, and an overlying lipid layer (Dilly, 1994; Gipson, 2004; Spurr-Michaud et al., 2007; Tiffany, 2008). Specialization of the apical surface membrane where it abuts the tear film facilitates the maintenance of fluids on the ocular surface. A heavily glycosylated glycocalyx formed by membrane-associated mucins extends

from the tips of surface ridges (microplicae). The extracellular domains of these mucins are shed constitutively into the tear film (Gipson, 2007; Gipson and Argueso, 2003; Govindarajan and Gipson, 2010; Khanal and Millar, 2010). The term "dacruon" has been coined for the combined fluids of the ocular surface (Cher, 2012).

The thickness of the tear film has also been under discussion (Rolando and Zierhut, 2001; King-Smith et al., 2000, 2004). There is evidence that the mucous layer of the film could be as thick as 30 μm, but a thinner film has also been hypothesized (King-Smith et al., 2000). Precise thickness measurements of the tear film using spectral domain optical coherence tomography showed the average thickness of the tear film over the central cornea to be 5.1 ± 0.5 μm (Schmoll et al., 2012). Alteration, deficiency, or loss of the tear film may significantly increase the susceptibility to ocular surface desiccation and infection, corneal ulceration and perforation, and marked visual impairment and blindness (Lamberts, 1983; Whitcher, 1987; Lubniewski and Nelson, 1990; Lemp and Marquardt, 1992; Lemp, 1995).

The Glycocalyx

Mucins can be divided into two subfamilies—the secreted gel-forming mucins and the membrane-tethered mucins. The three major membrane-tethered mucins produced by corneal and conjunctival epithelial cells are MUC1, MUC4, and MUC16 (Govindarajan and Gipson, 2010). The extracellular domains of MUC4 are constitutively shed into the tear film; thus, they are a component in the mucous/aqueous layer. The membrane-tethered mucins of the corneal and conjunctival glycocalyx are multifunctional proteins that (1) facilitate tear film spreading and ocular surface wetting; (2) act as an antiadhesive that prevents adherence of foreign debris, cells, or pathogens; (3) act as a selective barrier to the penetration of molecules; and (4) signal through their epidermal growth factor (EGF) domains or their cytoplasmic tails (Govindarajan and Gipson, 2010).

Aqueous Layer

Nearly 500 proteins have been identified in normal human tear fluid, including mucins, growth factors, tissue maintenance factors, and antimicrobial agents, the nature of which suggest contributions from serum exudate, lacrimal and accessory gland secretions, ocular surface components, and secreted products of PMN cells (Fung et al., 2002).

The largest part of the mucinous content of the tear film is MUC5AC, secreted by conjunctival goblet and epithelial cells into the tear fluid where they provide a scaffold for other defense molecules secreted by the lacrimal gland (Gipson and Inatomi, 1998; Jumblatt et al., 1999). The mucins, secreted by conjunctival goblet cells or released from the glycocalyx, account for the viscoelastic properties of the tear film, maintaining the dioptic integrity in the interblink period, and they minimize the trauma to the ocular surface during blinking (Dilly, 1985; Tiffany, 1994; Gipson, 2004). There is evidence that S-IgA and small, basically charged tear proteins such as lysozyme are associated with the soluble mucus in the aqueous layer (Chao et al., 1990; Bogart et al., 1994). The major sources of proteins in the tear aqueous layer are lacrimal and accessory lacrimal gland secretions. These secretions are derived from two independent processes: a slow constitutive ongoing secretion, consisting of almost exclusively secretory IgA and smaller amounts of free SC, and an inducible neurologically controlled lacrimal secretion.

Specific immunity at the ocular surface is mediated primarily through the action of IgA antibodies, which are the predominant Ig in tears of humans and experimental animals, occur almost entirely in polymeric form, and originate primarily from local production in lacrimal gland and conjunctival plasma cells (Chao et al., 1980; Janssen and van Bijsterveld, 1983; Sullivan and Allansmith, 1984; Peppard and Montgomery, 1987; Knop and Knop, 2003; Knop et al., 2008). In humans, tear IgA is distributed almost equally among IgA1 and IgA2 subclasses (Delacroix et al., 1982). Most tear IgA appears to be bound to, and transported by, SC, which is synthesized and secreted by lacrimal and conjunctival epithelial cells (Franklin et al., 1973; Gillette et al., 1980; Gudmundsson et al., 1985; Hann et al., 1989, 1991; Kelleher et al., 1991; Sullivan et al., 1998; Knop and Knop, 2003; Knop et al., 2008) and is present in the tear film as an S-IgA conjugate or as free SC. In addition, although tear Ig levels do not appear to display diurnal rhythms, IgA concentrations may be exceedingly high after prolonged closure of the eyelids (Sack et al., 2000, 2001). S-IgA has significant function in antigen–antibody clearance from the tear film. S-IgA or free SC can agglutinate antigen-IgG complexes (Sack et al., 2001). Furthermore, PMN cells have an S-IgA receptor and it appears that S-IgA can opsonize bacteria for PMN cell processing (Sibille et al., 1987; Nikolova and Russell, 1995), and S-IgA can also stimulate effector functions in eosinophils (Motegi and Kita, 1998). Antigen–IgA complexes will not ordinarily activate complement; therefore, S-IgA is considered anti-inflammatory in nature (Nikolova et al., 1994). The role of S-IgA may not be essential in antimicrobial defense because an SC knockout mouse does not exhibit a greater frequency of serious ocular or other mucosal infections (Johansen et al., 1999). However, lack of J chain inhibits transepithelial transport of IgA in knockout mice (Lycke et al., 1999).

Although complex, the inducible lacrimal secretion predominantly consists of four proteins—lysozyme, lactoferrin, tear-specific lipocalins (TSLs), and S-IgA—each of which exhibits anti-inflammatory and antimicrobial properties (Sack et al., 2001; also see Chapter 15). Lactoferrin represents 25% of the total reflex tear protein and has several functions. It enhances the function of natural killer cells,

it deprives bacteria of iron, and it inhibits the formation of biologically active complement by inhibiting the formation of C3 convertase (Arnold et al., 1982; Kijlstra et al., 1983; Kievits and Kijlstra, 1985; Mestecky and McGhee, 1987; Caccavo et al., 2002). The anti-inflammatory and antimicrobial functions of lactoferrin are attributed to its capacity to bind divalent cations and numerous ligands as well as its basically charged peptide sequence near the N-terminus. Lactoferrin inhibits complement activation, decreases the capacity of PMN cells to release oxygen radical species, and chelates iron, thereby depriving many bacteria of a necessary nutrient. Lactoferrin destabilizes the cell wall of Gram-negative bacteria by its chelation actions. The cationic detergent function of the highly basic N-terminal sequence (lactoferricin) disrupts the cell membrane of some Gram-negative bacteria (e.g., *Pseudomonas, Escherichia coli, Proteus*), *Staphylococcus aureus*, yeast, and filamentous fungi as well as some viruses including human immunodeficiency virus (HIV) and human cytomegalovirus (Kijlstra, 1990; Sack et al., 2000, 2001). Lactoferrin contributes to the regulation of immunity and inflammation via its capacity to interact directly with APCs, modulating migration and activation and affecting expression of cytokines, chemokines, and other effector molecules (Puddu et al., 2009).

Lysozyme represents approximately 33% of the reflex tear proteins. This enzyme cleaves the polysaccharide backbone of the murein layer of the bacterial cell wall as well as chitin in the fungal cell wall. Further, lysozyme can inhibit HIV transmission and inhibits complement activation (McClellan, 1997; Sack et al., 2000, 2001).

TSL is the predominant lipid carrier in tears and is critical to functions involving lipids in protecting the ocular surface (Dartt, 2011; Glasgow and Gasymov, 2011). TSL contain a putative functional cystatin-like protease inhibitory domain that has been suggested to protect the ocular surfaces from microbe-derived cysteine proteases. Other properties of TSL are consistent with an ocular defense function. Tear proteins, including lactoferrin, lysozyme, and S-IgA, complex with TSL. A lipid-binding domain allows TSL to transport lipids (e.g., retinol) essential for the maintenance of goblet and epithelial cell integrity. This domain may also allow the removal or sequestration of toxic lipids such as endotoxin (Glasgow et al., 1999). Furthermore, TSLs convert hydrophobic surfaces to hydrophilic ones, a property that may be useful in clearing hydrophobic foreign objects from the ocular surface and that affects tear surface tension (Gachon and Lacazette, 1998; Sack et al., 2000, 2001).

In addition, the open-eye tear fluid contains numerous other proteins that have anti-inflammatory and antimicrobial properties, including specific leukocyte protease inhibitor, elafin, and pro- and active members of the α- and β-defensin families. Other antimicrobial agents detected in the open-eye tear fluid include β-lysin, trefoil factor family peptides, CAP-37, CAP-38, phospholipase A2, and PMN cell defensins and elastase. In addition, antiproteases, various cytokines, vitronectin, and neutrophil gelatinase-specific lipocalin have been detected. At least 80 low-abundance bioactive proteins have been characterized in reflex, open-eye, and closed-eye tear samples (Sack et al., 2005). Characterization of 491 proteins in the tear fluid proteome by state-of-the-art spectrometric identification revealed many proteases and protease inhibitors, molecules involved in defensive mechanisms against pathogens, and extracellular matrix remodeling during wound healing (de Souza et al., 2006). When the rate of reflex tear secretion decreases, the constitutively secreted S-IgA becomes the fourth major protein constituent.

Overnight eye closure results in near cessation of inducible tear secretion, which is replaced by a constitutive-type secretion composed mainly of S-IgA. Eye closure is also associated with a subclinical inflammation as evidenced by an increase in vitronectin, elastase, α1-antitrypsin, specific leukocyte protease inhibitor, fibronectin, and albumin levels; the appearance of complement components C1q, C3, factor B, C4, C5, and C9; the conversion of complement C3 to C3c; plasminogen activation; the recruitment of PMN cells into the tear film; and an enhanced incidence of Gram-positive bacteria in the conjunctival sac (Sack et al., 2000, 2001, 2007). The closed-eye environment is conducive to extracellular remodeling as evidenced by 200-fold increases in matrix metalloproteinase-9 and its associated factors (Markoulli et al., 2012).

Lipid Layer

The principal role of the outer lipid layer is to prevent evaporation of the tears and enhance the stability of the tear film, thereby indirectly contributing to the antimicrobial nature of the tear film (Sack et al., 2001; Rolando and Zierhut, 2001). It consists of various lipid constituents, including waxy esters, triglycerides, free fatty acids, and polar lipids secreted by meibomian glands located within the tarsal plates (McCulley and Shine, 2001). For excellent, recent reviews see Bron et al. (2004) or Butovich (2011).

Other Defense Mechanisms

Other tissues and factors involved in nonspecific mucosal defense of the eye include the (1) orbital skeletal structure, which minimizes potential trauma; (2) eyelid architecture, which is relatively impermeable to macromolecules; (3) eyelid blink reflex and ciliary movement, which rapidly clear foreign objects from the ocular surface; and (4) continuous tear flow and reflex tearing, which act to remove microorganisms and cellular debris through hydrokinetics and eventual drainage into the nasolacrimal duct (Smolin, 1985). In addition, the presence of resident conjunctival populations of nonpathogenic bacteria, consisting of aerobes and facultative and obligate anaerobes, may curtail the

ability of invasive bacteria to attach and colonize. Colonization of the ocular surface epithelia is noninflammatory, allowing a peaceful coexistence between the two (Ueta, 2008). The normal flora depletes the tear fluid of nutrients, reacts with binding sites that might otherwise be available for pathogens, and secretes bacteriocidins that make the environment less hospitable for the growth of potential pathogens (Sack et al., 2001). As in the intestine (Cario, 2008) or skin (Cogen et al., 2008), crosstalk between commensal microbial flora and ocular epithelial cells and immunocytes may regulate several functions to maintain ocular surface health. These include barrier preservation, inhibition of inflammation and apoptosis, acceleration of wound repair, exclusion of pathogens, maintenance of immune tolerance, and linkage with the adaptive immune system (Miller and Iovieno, 2009).

INDUCTION OF OCULAR MUCOSAL IMMUNITY

Mucosal immunity constitutes an important first line of defense that protects the surfaces of the aerodigestive and urogenital tracts as well as the ocular surface. The various mucosal effector sites are linked by migrating lymphocytes, which give rise to IgA antibody-producing cells. The major features of the mucosal immune network, including the relevance of the mucosal system in immune defense, are detailed in several publications (Mestecky and McGhee, 1987; Childers et al., 1989), including this volume. The conjunctiva, lacrimal drainage apparatus, and the lacrimal glands fulfill the criteria for inclusion in the common mucosal immune system. As detailed above, CALT in humans and many species functions as an antigen-sampling and, along with its draining lymph nodes, an immune-inductive tissue. The nasal-associated lymphoid tissue (NALT) and the LDALT also receive antigen after application to the conjunctival sac and serve as immune-inductive sites (Carr et al., 1996; Ridley Lathers et al., 1998; Knop and Knop, 2001; Nagatake et al., 2009). The conjunctiva serves as a mucosal immune effector site (Franklin and Remus, 1984; Franklin, 1989; Knop and Knop, 1996, 2000; Knop et al., 2008). The lacrimal gland functions as a mucosal effector tissue, receiving antigen-stimulated, IgA-committed B cells after antigen stimulation in the intestinal Peyer's patches or other mucosal inductive sites (Franklin et al., 1985). It contains IgA-secreting plasma cells, which are responsible for most S-IgA released into the tear fluid.

Response to Defined Antigens

Antigenic challenge to the surface of the eye may result in a marked accumulation of specific S-IgA, IgG, and IgM antibodies in tears; an accelerated and enhanced anamnestic response after secondary exposure; and the generation of immune resistance to, and protection against, antigen reexposure (Mestecky et al., 1978). In addition, definitive ocular immune responses, as well as accumulation of Ig-containing cells in lacrimal tissue (Jackson and Mestecky, 1981; Allansmith et al., 1987), may be stimulated by antigenic challenge to other sites, including subconjunctival, intracorneal, intravitreal, intranasal, oral, intrabronchial, gastric, intraduodenal, intravenous, subcutaneous, intradermal, or intramuscular routes. The nature (e.g., antibody isotype), extent, and kinetics of these immune reactions appear to be dependent on the form (e.g., live vs inactivated microorganisms; strain), concentration, route, duration, and frequency of antigen administration. Potential immune responses may be augmented, intermittent, suppressed, or absent, as reviewed in Montgomery and Whittum-Hudson (1996). Moreover, the magnitude of induced ocular immunity may be altered by the use of adjuvants (Peppard et al., 1988; Peppard and Montgomery, 1990), cytokines (Pockley and Montgomery, 1991; Rafferty et al., 1996), immunostimulatory DNA (Gill and Montgomery, 2002), and microspheres (Rafferty et al., 1996; Ridley Lathers et al., 1998) and influenced by the concurrent state of systemic immunity (Waldman and Bergmann, 1987).

The mechanism by which antigenic exposure to the surface of the eye stimulates a local immune (e.g., IgA) response remains to be elucidated. Direct antigen transfer across the conjunctival epithelium or countercurrent passage through the lacrimal duct appears to be severely restricted (Huang et al., 1989; Kahn et al., 1990; Sullivan et al., 1998). Furthermore, the immunologic architecture of healthy lacrimal tissue appears to limit its capacity to effectively process and present antigen (Wieczorek et al., 1988). With respect to conjunctival tissue, it is now evident that it is endowed with lymphoid tissue capable of antigen uptake and processing, as is the lacrimal drainage system (Knop and Knop, 2001, 2002a,b; Paulsen, 2003; Paulsen et al., 2000, 2002, 2003; Nagatake et al., 2009). It was once postulated that the ocular secretory immune response to infectious or toxic substances may require antigenic clearance through the nasolacrimal duct and stimulation of intranasal and gut-associated lymphoid tissue. Consistent with the hypothesis that NALT is required for the induction of tear IgA antibody responses are the following observations: (1) topical application of noninvasive antigens to the rat ocular surface appears to result in passage through the nasolacrimal canal into the gastrointestinal tract, and not retrograde transfer to the lacrimal gland or lymphatic drainage into local lymph nodes (Sullivan et al., 1998). Likewise, herpes simplex virus in human tears has been shown to flow through the lacrimal canaliculi into the nasal cavity (Yoshida and Hondo, 1992); (2) intranasal, oral, or gastric administration of bacteria, viruses, or other antigens may induce the accumulation of specific tear IgA antibodies

and the generation of ocular surface protection (Mestecky et al., 1978; Nichols et al., 1978; Montgomery et al., 1983, 1984a; Bergmann et al., 1986; Waldman and Bergmann, 1987; Czerkinsky et al., 1987; Van Zaane et al., 1987; Peppard et al., 1988; Peppard and Montgomery, 1990; Davidson et al., 1993; Carr et al., 1996; Noriega et al., 1996; Montgomery and Rafferty, 1998; Ridley Lathers et al., 1998; Gill and Montgomery, 2002). On the other hand, recent studies now indicate that particulate antigen can be taken up by the conjunctiva and transported to the draining lymph nodes, showing that NALT is not an absolute requirement for the induction of rat tear IgA responses (Gill et al., 2010).

Remote-site stimulation would most likely involve IgA lymphoblast migration from nasal- or gastrointestinal-associated lymphoid tissue, and from cervical or mesenteric lymph nodes, via the thoracic duct lymph, to the lacrimal gland (Montgomery et al., 1983, 1985; McGee and Franklin, 1984; O'Sullivan and Montgomery, 1990; Montgomery and Whittum-Hudson, 1996), followed by local antibody production and transport to the ocular surface. In contrast, the contribution of serum IgA antibodies to ocular surface defense appears to be minimal or nonexistent (Sullivan and Allansmith, 1984; Montgomery et al., 1984b; Bergmann et al., 1986; Peppard and Montgomery, 1987; Czerkinsky et al., 1987). However, IgG antibodies from serum may serve a significant role in certain inflammatory disorders of the eye (Gupta and Sarin, 1983; Mackie and Seal, 1984; Wilhelmus et al., 1986). Overall, ocular immune protection may be conferred by local and distant antigenic exposure, with lacrimal and conjunctival tissue acting as recipients of committed IgA-containing cells that elaborate antigen-specific antibodies. However, the development of an optimal strategy to promote secretory immunity in the eye has yet to be established.

Influence of Ocular or Systemic Disease and Contact Lens Wear

Various ocular and systemic diseases, as well as contact lens wear, may significantly influence secretory immune expression in the human eye. Bacterial, viral, and fungal infections of the ocular surface, exposure to allergens, endocrine abnormalities, or graft versus host disorders may significantly increase or decrease levels of specific antibodies, total Igs, complement proteins, and nonspecific immune factors or induce changes in the lymphocytic profile of the conjunctiva. Of interest, if pathologic alterations are evident in only one eye, then immune responses may (Shani et al., 1985) or may not (Centifanto et al., 1989) occur in the contralateral, unaffected eye. With regard to contact lenses, these may bind (Gudmundsson et al., 1985) and cause modifications in the concentration of immune components in the tear film. The precise immunologic effects may depend on the composition of lens material, the efficacy of cleaning regimens, and/or the length of wear (Mannucci et al., 1984; Vinding et al., 1987). Recent studies indicate that multipurpose contact lens solutions contribute to an increase in corneal infections by destroying the membrane-bound mucin layer (Gordon et al., 2011).

In contrast, such conditions as IgA deficiency, ocular surgery, keratoconjunctivitis sicca, keratoconus, malnutrition, some infections, or autoimmune disease may often suppress ocular mucosal immunity. For example, pigmentary keratitis has been linked to tear S-IgA insufficiency (Fullard et al., 1995), and severe malnutrition may lead to a significant decrease in tear IgA and SC concentrations, a diminished number of IgA-containing cells in lacrimal tissue, and a blunted S-IgA antibody response to infectious challenge (Watson et al., 1985; Sullivan et al., 1990b). People with keratoconus were found to have lower levels of total protein, lactoferrin, and S-IgA in their tears (Balasubramanian et al., 2012). Furthermore, in striking contrast to other mucosal infections, HIV-1 does not induce strong, specific IgA responses in any body fluid, including tears (Mestecky et al., 2004).

Autoimmune disorders such as multiple sclerosis or Sjögren's syndrome may significantly alter or disrupt immune function in the eye. Multiple sclerosis, an auto-immune disease of possible viral origin, is associated with heightened levels of monomeric IgA and reduced amounts of SC in the tears of afflicted individuals (Coyle, 1989). Sjögren's syndrome, an autoimmune disease that occurs almost exclusively in females, is characterized by a progressive lymphocytic infiltration into the lacrimal gland, an immune-mediated destruction of lacrimal acinar and ductal epithelial cells, decreased tear IgA content, and keratoconjunctivitis sicca (Moutsopoulos and Talal, 1987; Kincaid, 1987; Homma et al., 1994; Sullivan, 1994). Furthermore, in experimental models of this complex disorder, the generation of autoantibodies (Ohashi et al., 1985) and autoreactive T cells to (Tsubata et al., 1996), and the deposition of IgG, IgA, and complement in ductal epithelial cells of (deLuise et al., 1982), lacrimal tissue may accompany the striking glandular inflammation (Jabs et al., 1985; Jabs and Prendergast, 1988; Tsubata et al., 1996; Takahashi et al., 1996; Sullivan et al., 1997; Robinson et al., 1998; van Blokland and Versnel, 2002). The etiology of Sjögren's syndrome may involve the endocrine system (Ansar et al., 1985; Talal and Ahmed, 1985; Nelson and Steinberg, 1987; Ahmed et al., 1989; Homo-Delarche et al., 1991; Homo-Delarche and Durant, 1994; Sullivan, 1994, 1997; Sullivan et al., 1997, 1999), but it may also be due to primary infection by, and reactivation of, Epstein–Barr virus, cytomegalovirus, herpes virus-6, hepatitis C, or retroviruses (Burns, 1983; Fox, 1988; Green et al., 1989; Krueger et al., 1990; Mariette et al., 1991, 1993; Fox et al., 1991; Pflugfelder et al., 1993; Pepose et al., 1996; Sipsas et al., 2011). These viruses have been identified in

the lacrimal and/or salivary tissues of Sjögren's patients (Burns, 1983; Fox et al., 1986; Fox, 1988; Krueger et al., 1990; Garry et al., 1990; Mariette et al., 1991; Pflugfelder et al., 1993; Tsubota et al., 1995; Pepose et al., 1996) and may possibly stimulate the inappropriate epithelial cell human leukocyte antigen-DR and Toll-like receptor expression, T helper/inducer cell activation, B cell hyperactivity, and autoantibody production evident in these affected tissues (Moutsopoulos and Talal, 1987; Maini, 1987; Fox, 1988; Homma et al., 1994; Berglova et al., 2011; Lambiase et al., 2011). In support of this possibility, certain viral infections in experimental animals exert a striking effect on the lacrimal gland and induce a periductular infiltration of plasma cells, lymphocytes, and macrophages; distinct nonsuppurative periductular inflammation; significant interstitial edema; widespread necrosis of the acinar and ductal epithelium; degenerative and atrophic alterations in epithelial cells; diminished tear flow; and keratoconjunctivitis sicca (Jacoby et al., 1975; Green et al., 1989). Moreover, herpes viruses (i.e., cytomegalovirus) and coronaviruses (i.e., sialodacryoadenitis virus) may invade and replicate in rat lacrimal gland acinar cells (Huang et al., 1996; Wickham et al., 1997), Epstein–Barr virus may bind to specific receptors in ductal epithelium of the human lacrimal gland (Levine et al., 1990), and HIV infection may predispose patients to keratoconjunctivitis sicca (Couderc et al., 1987; Ulirsch and Jaffe, 1987; De Clerck et al., 1988; Lucca et al., 1990; Neves et al., 1994). The precise role of viruses in the induction of autoimmune disease, as well as the mechanism by which viral infection may interfere with lacrimal gland function and immune expression, is becoming understood. There is increasing evidence that environmental factors such as viral infection or hypoestrogenism trigger Sjögren's syndrome in persons carrying susceptibility genes that predispose enhanced innate immunity via type 1 IFN pathway proteins, leading to activation of lacrimal and salivary gland epithelial cells. Subsequent autoantigen presentation by the epithelial cells leads to T cell activation and overproduction of B cell activating factor, induced by IFN, and stimulates B cell activation and initiation of adaptive immunity as well as the production of autoantibodies (Manoussakis and Kapsogeorgou, 2010; Mavragani and Crow, 2010; Low and Witte, 2011).

Neuroendocrine Modulation

For many years it has been recognized that the endocrine and nervous systems regulate multiple aspects of cellular and humoral immunity. This hormonal and neural control, which significantly influences such parameters as lymphocyte differentiation and maturation, antigen presentation, cytokine production, cell migration, and antibody synthesis, is regulated by two major mechanisms: (1) the hormonal stress response with the production of glucocorticoids and (2) the autonomic nervous system with the release of noradrenalin (Webster et al., 2002; Sternberg, 2006). The central nervous system can also regulate the immune system locally via the release of neuropeptides from peripheral nerves and by locally produced corticotrophin-releasing hormone (Elenkov et al., 2000; Wrona, 2006; Nance and Sanders, 2007; Levite, 2008; Thayer and Sternberg, 2010; Levite, 2000, 2008). Moreover, this neuroendocrine-immune interrelationship is bidirectional, and antigenic exposure may also induce the lymphocytic secretion of cytokines, hormones, and neuropeptides that directly modulate endocrine and neural function (Mulla and Buckingham, 1999; Besedovsky and del Rey, 2000; Smith, 2008). In fact, it has been proposed that the immune system serves as a sensory organ, providing input to the endocrine and nervous compartments in response to noncognitive stimuli, such as infection (Blalock, 1984; Blalock and Smith, 2007). Consequently, an extensive, triangular association appears to exist between the endocrine, nervous, and the innate and adaptive immune systems that acts to promote and maintain homeostasis (Befus et al., 1999; Petrovsky, 2001; Webster et al., 2002; Eskandari and Sternberg, 2002; Sternberg, 2006; Irwin and Cole, 2011).

Likewise, in the mucosal immune system, diverse hormones and neural agonists may significantly modify the (1) accumulation, proliferation, retention, and/or function of various innate and adaptive immune system cells; (2) synthesis and expression of IgA and IgG antibodies, growth factors, cytokines, adhesion molecules, apoptotic factors, MHC class II antigens, SC, and the uptake and transport of pIgA into luminal secretions; and (3) adherence and presentation of microorganisms to mucosal cells, the magnitude of neurogenic inflammation, and the extent of local immune protection against infectious agents. In addition, antigen-induced immune responses may significantly alter mucosal neuroendocrine structure, sensitivity, and/or function (Stead et al., 1987, 1991; Weisz-Carrington, 1987; Bienenstock, 1993; Wira and Prabhala, 1993; Wood, 1993; Lambert et al., 1994; Gao et al., 1995; Sullivan and Edwards, 1997; Sullivan, 1997; Sullivan et al., 1998; Befus et al., 1999; Di Comite et al., 2007).

Sex and sex hormones influence the lacrimal system, eyelids and blinking, corneal anatomy and disease, aqueous humor dynamics and glaucoma, crystalline lens and cataract, uveitis and retinal disease, ocular circulation, and optic nerve anatomy and disease (Wagner et al., 2008). With regard to the ocular mucosal immune system, endocrine (androgens, but not estrogens or stress hormones) and neural factors appear to exert a dramatic effect on immunologic expression and activity. This neuroendocrine-immune interrelationship has been definitively shown in the eyes of experimental animals and is likely to occur in humans (Khandelwal et al., 2012). In rats, androgens elicit a marked increase in the production and secretion of SC by lacrimal

gland acinar cells (Hann et al., 1991; Kelleher et al., 1991; Lambert et al., 1994; Sullivan et al., 1998), enhance the concentration of IgA in lacrimal tissue (Sullivan et al., 1998), and stimulate the transfer and accumulation of SC and IgA, but not IgG, in tears (Sullivan and Edwards, 1997; Sullivan et al., 1998). These hormone actions, which may be induced by various androgenic compounds (Sullivan et al., 1998), are not duplicated by estrogen, progestin, glucocorticoid, or mineralocorticoid treatment (Sullivan and Edwards, 1997; Sullivan et al., 1998). Moreover, the immunologic effects of androgens appear to be unique to the eye because androgen administration does not seem to influence IgA or SC levels in salivary, respiratory, intestinal, uterine, or bladder tissues (Sullivan et al., 1998) and actually suppresses mucosal immunity in the mammary gland (Weisz-Carrington et al., 1978). The mechanism by which androgens regulate ocular SC dynamics may well involve hormone association with specific nuclear receptors in lacrimal gland acinar cells, binding of these androgen/receptor complexes to genomic acceptor sites, and the promotion of SC mRNA transcription and translation. In support of this hypothesis, saturable, high-affinity, and androgen-specific receptors, which adhere to DNA, have been identified in lacrimal tissue (Ota et al., 1985; Sullivan et al., 1998). In addition, androgens increase SC mRNA levels in lacrimal glands (Gao et al., 1995). Androgen-induced SC production by acinar cells may be inhibited by androgen receptor (cyproterone acetate), transcription (actinomycin D), or translation (cycloheximide) antagonists (Lambert et al., 1994). In contrast, the in vivo processes underlying androgen action on IgA in the rat eye, as well as this hormone's enhancement of tear IgA levels in the mouse (Sullivan and Edwards, 1997), remain to be determined. Although estrogen and progesterone regulate numerous genes in the mouse lacrimal gland, they do not appear to be a major factor underlying the sexual dimorphism of gene expression in lacrimal tissue (Suzuki et al., 2006). In contrast, testosterone regulates the expression of over 2000 genes in lacrimal and meibomian glands and in meibomian and conjunctival cells, and androgen action is mediated through classical androgen receptors and may contribute to the sex-related differences in gene expression in the lacrimal gland (Richards et al., 2005, 2006; Sullivan et al., 2009). This may explain the pronounced, sex-related differences in the rat ocular secretory immune system, in which the number of IgA-containing cells, and the IgA and SC output, are significantly greater in adult male lacrimal tissue as compared with that of adult females. This sexual dimorphism also extends to tears, in which from puberty to senescence, free SC and IgA, but not IgG, occur in considerably higher levels in male rats (Sullivan and Allansmith, 1988; Sullivan et al., 1998). Indeed, androgen influence may well be involved in the distinct sex-associated differences in the structural appearance, histochemistry, biochemistry, immunology, and molecular biologic expression of the lacrimal gland in various species, including mice, hamsters, guinea pigs, rats, rabbits, and humans (Waterhouse, 1963; Cavallero, 1967; Hahn, 1969; Lauria and Porcelli, 1979; Cornell-Bell et al., 1985; Cripps et al., 1986; Sullivan and Allansmith, 1988; Hann et al., 1988; Pangerl et al., 1989; Mircheff et al., 1991; Azzarolo et al., 1993; Gao et al., 1995; Sullivan et al., 1997, 1998; Toda et al., 1999; Rocha et al., 1997; Marcozzi et al., 2000; Madia et al., 2001; Richards et al., 2002; Liu et al., 2002a).

With respect to humans, sex appears to influence the (1) degree of lymphocyte accumulation in the lacrimal gland (Waterhouse, 1963); (2) IgA concentrations in tears of adults (Sen et al., 1978), but not the elderly (Sand et al., 1986); (3) the levels of TGF-α and EGF in tears (van Setten and Schultz, 1994; Barton et al., 1998); and (4) the frequency of Sjögren's syndrome-related lacrimal gland immunopathology (Moutsopoulos and Talal, 1987; Kincaid, 1987; Fox, 1992; Homma et al., 1994; Sullivan et al., 1997, 1999). Of interest, androgen administration to animal models of Sjögren's syndrome (i.e., MRL/Mp-lpr/lpr and NZB/NZW F1 female mice) dramatically suppresses the inflammation in, and significantly stimulates the functional activity (e.g., IgA output) of, lacrimal tissue (Sullivan and Edwards, 1997; Sullivan et al., 1997, 1998). This hormone effect appears to be tissue specific and mediated through a hormone interaction with receptors in epithelial cell nuclei, causing altered expression and/or activity of cytokines, proto-oncogenes, and apoptotic factors (i.e., TGF-β1, IL-1 β, TNF-α, c-myb, bcl-2, and Bax) in the lacrimal gland (Wickham et al., 1996; Sullivan et al., 1997; Toda et al., 1999; Rocha et al., 1997). It is likely that the sex steroids are produced locally, as indicated by the presence of the enzymatic machinery necessary for the synthesis and metabolism of sex steroids in human lacrimal gland, meibomian gland, cornea, and conjunctiva (Schirra et al., 2006).

In addition to androgens, the hypothalamic-pituitary axis appears to play an important role in the expression of the ocular secretory immune system. Disruption of this axis by hypophysectomy or extirpation of the anterior pituitary of the rat significantly reduces the number of IgA plasma cells in lacrimal tissue; diminishes the acinar cell production of SC, causes a striking decrease in the levels of tear IgA and SC; and almost completely curtails androgen action on ocular mucosal immunity (Gao et al., 1995; Sullivan et al., 1998). Moreover, this endocrine disturbance has a marked effect on lacrimal gland structure and function, leading to glandular atrophy, acinar cell contraction, nuclear pycnosis, cytoplasmic vacuolar metamorphosis, a decrease in tissue protein and mRNA content, and a decline in fluid and protein secretion (Azzarolo et al., 1992; Sullivan et al., 1998). The physiologic mechanisms responsible for hypothalamic-pituitary involvement in the ocular secretory immune system remain to be elucidated, but they may include numerous neuroendocrine and immunologic pathways. The hypothalamus and pituitary regulate multiple endocrine circuits, directly influence

neural innervation in the lacrimal gland, and clearly modulate immune activity (Berczi, 1990; Berczi and Nagy, 1990). Furthermore, the hypothalamic-pituitary axis is known to control many hormones, neurotransmitters, and cytokines that modify androgen and acinar cell function and control mucosal immunity (Mooradian et al., 1987; Sullivan et al., 1998). Other studies in humans or experimental animals demonstrated that (1) sex steroids may significantly alter the development of allergic conjunctivitis in rabbits (Saruya, 1968); (2) diabetes may enhance the incidence of keratoconjunctivitis sicca (Ramos-Remus et al., 1994) and significantly diminish the expression of the secretory immune system of the eye, most likely related to the absence of insulin (Jackson and Hutson, 1984; Hann et al., 1991; Sullivan et al., 1998); and (3) both the thyroid and adrenal glands are essential to achieve the full magnitude of androgen-induced effects on the secretory immune system of the eye (Sullivan et al., 1998).

With respect to neural regulation of ocular mucosal immunity, the stromal, periductal, perivascular, and/or acinar areas of lacrimal tissue are innervated by many parasympathetic, sympathetic, and peptidergic fibers that harbor numerous immunoactive transmitters, including vasoactive intestinal peptide (VIP), substance P, neuropeptide pituitary adenylate cyclase-activating peptide, methionine enkephalin, leucine enkephalin, calcitonin gene-related peptide, neuropeptide Y, dopamine, 5-hydroxytryptamine, and adrenergic and cholinergic agents (Ruskell, 1971; Nikkinen et al., 1984; Walcott, 1990; Dartt, 1992; Williams et al., 1994; Seifert et al., 1996). These neural agonists are known to control lymphocyte retention and/or function in other mucosal sites (Ottaway, 1984; Walcott et al., 1986; Stanisz et al., 1986; Freier et al., 1987; Hart et al., 1990; D'Orisio and Panerai, 1990; Bienenstock, 1993; Homo-Delarche and Durant, 1994; Chrousos, 1995; Wilder, 1995; Besedovsky and del Rey, 1996), and their release may well influence the adherence, distribution, or activity of IgA plasma cells, T cells, or mast cells in the lacrimal gland (Franklin et al., 1988; Oeschger et al., 1989; Franklin et al., 1989; Williams et al., 1994). Consistent with this possibility, VIP appears to augment T cell attachment to murine lacrimal tissue (Oeschger et al., 1989), and systemic administration of the β-adrenergic blocker, practolol, suppresses human tear IgA levels (Garner and Rahi, 1976). However, the nature of the sympathetic–immune interaction requires further clarification because ocular application of the β-blocker, timolol, to humans and sympathetic denervation in rats (Sullivan et al., 1990a) had no apparent effect on tear IgA content. Recent studies indicate that VIP has an indirect effect on IgA secretion by stimulating dendritic cells to produce IgA inducing protein, which promotes class-switching of IgD^+ B cells to IgA^+ cells (Austin et al., 2003; Endsley et al., 2009; Estes, 2010).

Conversely, it has been demonstrated that VIP and the β-adrenergic agent, isoproterenol, directly increase basal- and androgen-stimulated SC production by rat acinar epithelial cells (Kelleher et al., 1991; Lambert et al., 1994). This neural regulation of SC synthesis may be mediated through the modulation of intracellular adenylate cyclase and cyclic adenosine monophosphate (cAMP) activity. In support of this hypothesis, VIP and adrenergic agents are known to enhance the generation of cellular cAMP (Mauduit et al., 1984; Dartt, 1989, 1992). Furthermore, exposure of lacrimal gland acinar cells to cAMP analogues, cyclic AMP inducers (i.e., prostaglandin E_2 and cholera toxin), or phosphodiesterase inhibitors may elevate SC production (Kelleher et al., 1991). This cAMP influence on SC elaboration, although pronounced in the lacrimal gland, is not necessarily reproduced in other mucosal epithelial cells (Lambert et al., 1994). Of interest, cAMP and cyclic guanine monophosphate appear to increase S-IgA output by human main and accessory lacrimal glands in vitro (Hunt et al., 1996). However, the mechanism underlying this cyclic guanine monophospate action is unclear given that this compound has no effect on SC production by rat lacrimal gland acinar cells (Kelleher et al., 1991).

Cholinergic agonists also modulate the ocular secretory immune system. In humans, parasympathetic agents stimulate the secretion of EGF and TGF-β1 from the lacrimal gland (Yoshino et al., 1996a,b), whereas in birds, carbachol, by apparently binding to muscarinic acetylcholine receptors on IgG plasma cells, increases IgG output from the Harderian gland (Brink et al., 1994; Cameron et al., 1995). In contrast, carbamylcholine (carbachol) acutely (i.e., hours) enhances, but chronically (i.e., days) decreases, basal-, cholera-toxin-, and androgen-induced SC production by rat lacrimal gland acinar epithelial cells (Kelleher et al., 1991; Lambert et al., 1994). The transient effect of this compound may be mediated through the mobilization of intracellular calcium, the activation of protein kinase C, and the rapid enhancement of cellular secretion (Dartt, 1989; Lambert et al., 1994). The processes underlying the long-term inhibitory action of carbachol, which may be prevented by atropine, is unknown, but it may involve the suppression of cAMP (Jumblatt et al., 1990) or an alteration of gene activity (Lambert et al., 1994).

The mucosal immune system of the eye may also be regulated by cytokines. For example, IL-1α, IL-1β, and TNF-α, but not IL-6 or IFNγ, stimulate the acinar cell synthesis and secretion of SC (Kelleher et al., 1991). The regulatory effect of TNF-α on acinar cell SC is similar to that found in colonic cell lines, in which TNF-α, IFNγ, and IL-1 increase the production, surface expression, and release of SC (Kvale et al., 1988). However, the absence of IFNγ activity on SC output by acinar cells is notable in that this cytokine regulates SC dynamics in intestinal (Sollid et al., 1987; Kvale et al., 1988; Nilsen et al., 1999; Blanch et al., 1999) and uterine (Wira and Prabhala, 1993) epithelial cells and may influence lacrimal gland acinar cell secretion (Lambert, 1998). Although IL-6 appears to have no influence on lacrimal SC production (Kelleher et al., 1991), IL-6 and IL-5 stimulate the synthesis of IgA in lacrimal tissue explants (Pockley and Montgomery, 1990b) and in combination augment the secondary tear IgA

antibody response to pneumococcal antigen (Pockley and Montgomery, 1991) and suppress IgG and IgM synthesis in lacrimal tissue (Pockley and Montgomery, 1990a). Likewise, TGF-β enhances IgA output from rat lacrimal tissue, whether alone or in combination with IL-2, IL-5, IL-6, or IL-5 plus IL-6 (Rafferty and Montgomery, 1993). However, TGF-β or IL-4 also inhibits lymphocyte binding to lacrimal gland acinar epithelium (Elfaki et al., 1994).

As further considerations, androgen-, VIP-, IL-1-, and Th17-mediated responses all share the capacity to increase IgA production in various tissues (Drew and Shearman, 1985; Stanisz et al., 1986; Sullivan et al., 1998; Jaffar et al., 2009; Zheng et al., 2010). In turn, pIgA may heighten the monocytic output of TNF-α (Deviere et al., 1991). Th17 responses also upregulate pIgR expression, and thus S-IgA production, in the intestine (Cao et al., 2012). S-IgA binds selectively to M cells in Peyer's patches and can function in antigen delivery to dendritic cells in the underlying dome region to stimulate mucosal immune responses (Favre et al., 2005; Corthesy, 2007). If analogous activity occurs in the lacrimal gland, then various neuroimmunoendocrine factors may control the synthesis of IgA antibodies and the IgA receptor, leading to enhanced antibody transfer to tears and improved ocular surface defense.

OVERVIEW

In ocular mucosal immunity, the lacrimal gland is the principal effector site where secretory IgA antibodies are produced. These antibodies are transported, via the tears, to the ocular surface where they contribute to protection against allergic, inflammatory, or infectious disease and thus promote corneal and conjunctival health. NALT (the rodent equivalent of human Waldeyer's ring tissue) and its draining posterior cervical lymph node (CLN) acquire antigen and appear to function as a major inductive site for eliciting tear IgA responses after antigenic challenge to the external ocular compartments. It is thought that nonpenetrating antigen drains from the ocular surface via the nasolacrimal duct and is taken up by the M cells overlaying NALT. Alternately, antigen taken up by the conjunctiva is transported directly to the superficial CLN, thus following an alternative inductive pathway that bypasses the NALT and posterior CLN (summarized in Figure 3).

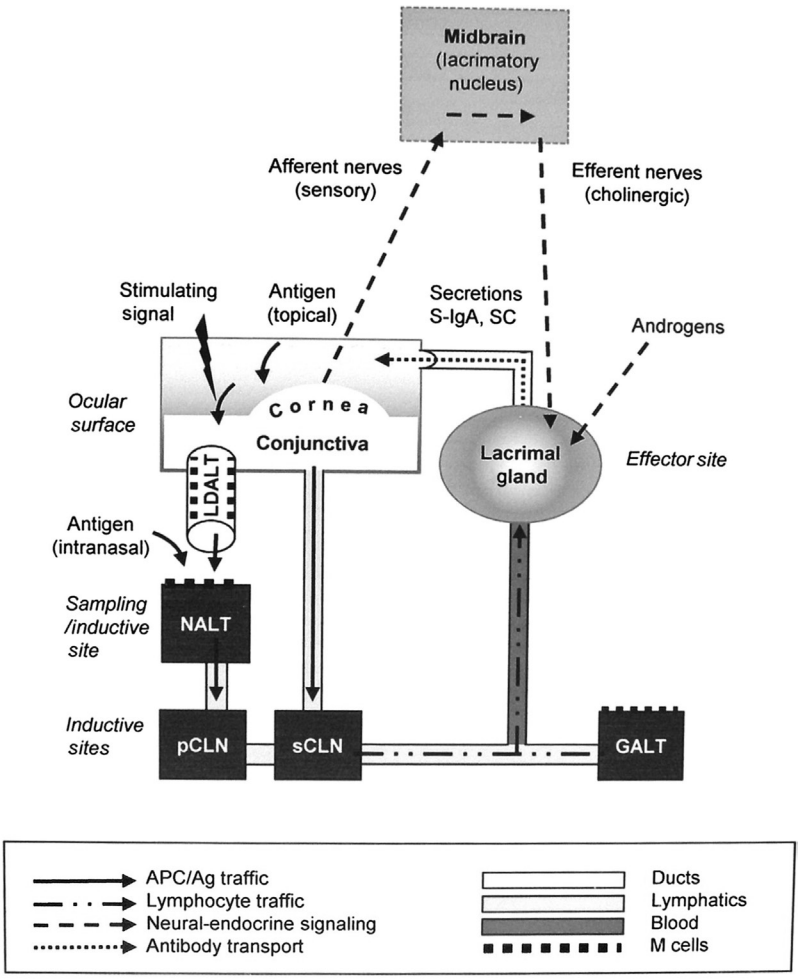

FIGURE 3 Schematic summarizing the ocular mucosal immune system and control of lacrimal gland function. Exogenous (microbe-derived) or endogenous (tissue-derived) stimulatory signals from antigen-challenged mucosal surfaces may be directed to sampling/inductive (conjunctiva, lacrimal drainage-associated lymphoid tissue (LDALT), nasal-associated lymphoid tissue (NALT), cervical lymph nodes (CLNs)) and effector (lacrimal gland) sites, resulting in the induction of protective mucosal immune responses. Mucosal surfaces are heavily innervated with afferent nerves leading to the midbrain (lacrimatory nucleus). Cortical input (including input from the gonadal axis) is also received in the midbrain nucleus; a net signal is integrated and then sent through efferent nerves to the lacrimal glands. Cholinergic nerves, using acetylcholine and vasoactive intestinal peptide as neurotransmitters, innervate the glands, whereas adrenergic fibers using norepinephrine go to blood vessels (not shown). The lacrimal glands contain M1 and M3 muscarinic acetylcholine receptors and produce secretions (tears) containing water and proteins (including S-IgA and SC) upon efferent stimulation. Sex hormones as well as various neurotransmitters and neuropeptides, via receptors on immunocytes, also influence the outcome of immune responses in the lacrimal gland. ACh, acetylcholine; mAChR, muscarinic acetylcholine receptor; Ag, antigen; M cell, microfold cell. *This figure has been modified and published courtesy of Academic Press; Mucosal Immunology, third edition.*

The tear film, lacrimal glands, corneal and conjunctival epithelia, and meibomian glands work together as a lacrimal functional unit. Neural connections and systemic hormones maintain the integrity and function of the ocular surface (Stern et al., 1998a,b; Lemp et al., 2007). The surface of the eye is heavily innervated, having more afferent nerves than the combined total in the rest of the body. Also, as diagrammed in Figure 3, conjunctival or corneal stimuli are sensed by afferent sensory neurons and the information relayed to the midbrain (lacrimatory nucleus), which also receives neural input from higher cortical regions. The net signal is "integrated" and efferent signals are sent to the blood vessels via adrenergic fibers (i.e., norepinephrine as a neurotransmitter) to release water to serve as the volume for tears. A separate set of cholinergic fibers (acetylcholine and VIP as neurotransmitters) is sent to the lacrimal glands and signal acinar and ductal cells (via the M3 muscarinic acetylcholine receptor) to pump aqueous secretion as tears (Fox and Stern, 2002). The normal lacrimal gland physiology is influenced by the sex hormone milieu (regulated by the hypothalamic-pituitary-gonadal axis).

Ocular infections can influence neural signaling in the lacrimal gland through induction of cholinergic enzymes, which reduce expression of acetylcholine and modulate receptors (muscarinic acetylcholine receptor) on acinar cells and on plasma cells, thereby decreasing fluid and Ig secretion (Dannelly et al., 2001). Responses involving T lymphocyte-dependent antigens have been shown to result in production of IL-4 in lacrimal glands and influence cholinergic enzyme activity (Sinha et al., 2001), affecting immune processes and lacrimal physiology. Further, neuropeptides released into lymphoid structures or inflamed tissues are known to be chemotactic for APCs and to affect their interactions with T cells (Lambrecht, 2001). Thus, it appears that consideration of the entire ocular compartment, including its connecting innervation, will be important in developing therapeutic approaches for treating dry-eye conditions and vaccination strategies for eliciting protective ocular mucosal immune responses.

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