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The mucosal immune system defends the ocular surface against antigenic challenge (Franklin, 1989; Montgomery et al., 1994; Montgomery and Whittum-Hudson, 1996; McClellan, 1997; Sullivan, 1999; Sack et al., 2001). This immunologic role is mediated primarily through secretory IgA (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 (Underdown and Schiff, 1986; Mestecky and McGhee, 1987; Childers et al., 1989; Ogra et al., 1999). Thus, the ocular mucosal immune system appears to protect 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 impact 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).

**ARCHITECTURE OF OCULAR MUCOSAL DEFENSES**

The epithelia of the cornea, the conjunctiva, and 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 and protect ocular structures. These components are in anatomic continuity and share feedback mechanisms whereby simultaneous reactions occur to a single stimulus (Rolando and Zierhut, 2001).

**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 the primary effector tissue in the eye's secretory immune defense (Sullivan and Allansmith, 1984; Peppard and Montgomery, 1987; Franklin, 1989; Montgomery and Whittum-Hudson, 1996; McClellan, 1997; Sullivan, 1999). It 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 (Fig. 86.1; Wieczorek et al., 1988). Smaller accessory lacrimal glands are also found in the upper and lower conjunctiva, which drain directly through the epithelium (Fig. 86.2; Sacks et al., 1986).

Lacrimal glands contain a diverse array of leukocytes, including plasma cells, T cells, B cells, lymphocytes bearing the human mucosal lymphocyte-1 antigen (HML-1, beta 7 integrin), dendritic cells, macrophages, monocytes, and natural killer cells (Table 86.1; Fig. 86.1). In humans, plasma cells represent greater than 50% of all mononuclear cells in lacrimal tissue, the vast majority being IgA-positive with both 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 secretory IgA (S-IgA), the major effector molecule in mucosal defense (Franklin et al., 1973; Allansmith and Gillette, 1980; Gillette et al., 1980; Crago et al., 1984; Allansmith et al., 1985; Brandzaeg, 1985; Underdown and Schiff, 1986; Kett et al., 1986; Mestecky and McGhee, 1987; Wieczorek et al., 1988; Childers et al., 1989). These cells are complemented by limited numbers of IgG, IgM, IgE, and IgD plasma cells (Allansmith et al., 1976a; Brandzaeg et al., 1979, 1987).

The second most frequent lymphocyte population in human lacrimal tissue are T cells, which are situated between acinar and ductal epithelial cells, throughout glandular inter-
stitial regions, and within small, periductular, lymphoid aggregates. The distribution of T cells varies topographically by subclass, which include CD8 + suppressor/cytotoxic and CD4 + helper T cells, which have a helper:suppressor ratio of approximately 0.5. Minor populations of lacrimal immunocytes include surface Ig-bearing B cells, Langerhans-type dendritic cells, monocyte-macrophages, and activated, IL-2-positive T cells, which occur almost exclusively in periductular foci, appearing as primary follicles without germinal centers (Wieczorek et al., 1988; Dua et al., 1994; Pepose et al., 1996). Lacrimal glands of rats, rabbits, and mice share the immune features of the human gland (see Table 86.1).

In addition to S-IgA, the lacrimal gland supplies a number of 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, lactoferrin, and β-lactamase, which have antibacterial properties. Lysozyme is a bacteriolytic enzyme that makes up 40% of tear protein (Gillette and Allansmith, 1980; Gillette et al., 1981). Although its existence in tears has been debated (Janssen et al., 1984), the nonlysozyme factor β-lactamase is also bacteriolytic (Ford et al., 1976). Lactoferrin makes up 25% of the protein in human tears and has several functions. It enhances the function of NK 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). Lacrimal glands also produce and secrete into the tears antimicrobial peptides including defensins (Haynes et al., 1998). 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. 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). Yet, 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, T-cell, and/or acinar epithelial cell signals (Jackson and Mestecky, 1981; Franklin et al., 1985; Crago et al., 1984; Wieczorek et al., 1988; Dua et al., 1994; Fujihara et al., 1999). The lymphocytic accumulation in, or adherence to, lacrimal tissue appears to require receptors, divalent cations, intact metabolic, oxidative phosphorylation, and contractile microfilament systems, and to depend upon cellular surface protein and carbohydrate determinants (O'Sullivan and Montgomery, 1990; O'Sullivan et al., 1994a, 1994b, 1995).

Conjunctiva

The conjunctival tissue consists of an outer squamous epithelial cell layer (two to five cells thick) interspersed with goblet cells, a basement membrane, and underlying stromal connective tissue. Figure 86.2 (Sacks et al., 1986) diagrams the major features of the human conjunctiva. The conjunctiva has been postulated to possess a system of specific immune defense in the form of mucosa-associated lymphoid tissue (MALT) (Chandler and Gillette, 1983). MALT consists of arrangements of lymphatic cells located in and closely beneath the epithelium, which function to detect antigen and induce immune responses by the direct action of the lymphatic cells or by the secretion of soluble antibodies (Kraehenbuhl and Neutra, 1992). The presence of conjunctiva-associated lymphoid tissue (CALT) has been uncertain. In some animal species, components of MALT 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, 1998b; Chodosh and Kennedy, 2002). Early human studies using histochemical methods (Kessing, 1968; Allansmith et al., 1978) and more recent immunohistochemical studies analyzing small biopsy specimens (Sacks et al., 1986; Dua et al., 1994; Hingorani et al., 1997) reported differing results as to number and localization of the cells, which did not clearly establish whether conjunctival lymphoid cells formed a functionally active CALT.
system. Recently, Knop and Knop (2000) analyzed whole mounts of normal human conjunctival sacs and determined the associated lymphoid tissue contains all the components necessary for an immune response and that expression of IgA and secretory component indicates that 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 the conjunctival sacs. The overlying epithelium produced secretory component. 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 microvilli of conjunctival FAE and that of nonfollicle-associated epithelium were noted by transmission electron microscopy in 13 mammalian species (Chodosh et al., 1998b; Chodosh and Kennedy, 2002). 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), although MALT has recently been demonstrated in nictitating membranes of mice (Sakimoto et al., 2002). Similar lymphoid tissue was also observed inside the lacrimal drainage system and has been termed lacrimal drainage-associated lymphoid tissue (LDALT) (Knop and Knop, 2001). 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 and a reduced amount under germfree conditions (McMaster et al., 1967). 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 may form a functional unit connected by tear flow, lymphocyte migration, and probably the neural reflex arc, and play a major role in preserving ocular surface integrity (Knop and Knop, 2000; Rolando and Zierhut, 2001; Knop and Knop, 2001). In addition, 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).

**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, PAI-2, and 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 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 to 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), recent 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 MHC class II-negative population of resident corneal Langerhans-type dendritic cells has been identified in the central cornea (Hamrah et al., 2002). 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). In inflammation these dendritic cells become activated, as evidenced by expression of B7 costimulatory markers, and following corneal transplantation, 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 lack of resident lymphoepithelial 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-1\(\beta\) is secreted by corneal epithelial cells in response to IFN\(\gamma\) or bacterial infection (Wakefield and Lloyd, 1992). Further, normal keratocytes express MHC class II molecules in response to inflammation, suggesting that keratocytes collaborate with APC 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 TGF-\(\beta\), IL-1, IL-6, and TNF-\(\beta\) that
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 upon the stability, tonicity, and composition of the tear film structure, the actual architecture of which is not totally resolved. Classically, the tear film has been considered to include an underlying mucin foundation, a middle aqueous component, and an overlying lipid layer (Holly, 1987; Whitcher, 1987; Dartt, 1992). Recently, a two-layered structure with an underlying aqueous-mucin gel, in which the mucins have a decreasing gradient of concentration from the epithelium to the surface, and an overlying lipid layer, has been proposed (Dilly, 1994). The thickness of the tear film is also under discussion (Rolando and Zierhut, 2001). 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. Recent evidence suggests a 3 μm thickness for the tear film (King-Smith et al., 2000). 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 mucous layer and IgA**
The largest part of the mucinous content of the tear film is produced by conjunctival goblet and epithelial cells, and closely adheres to the surface of the globe. The major mucin species is MUC5AC, present in a variety of molecular sizes and glycoforms (Gipson and Inatomi, 1998; Jumblatt et al., 1999). The corneal and conjunctival epithelial cells produce a mucinlike glycoprotein (MUC1) at the apical surfaces that constitute a glycocalyx, which binds loosely to the mucin layer (Gipson and Inatomi, 1998). This transmembrane mucin facilitates tear film spreading and ocular surface wetting and prevents adherence of foreign debris, cells, or pathogens to the ocular surface. The mucins account for the viscoelastic properties of the tear film, maintaining the dioptric integrity in the interblink period, and minimize the trauma to the ocular surface during blinking (Dilly, 1985; Tiffany, 1994). There is evidence that S-IgA and small, basically charged tear proteins such as lysozyme accumulate in the ocular mucin layer (Chao et al., 1990; Bogart et al., 1994).

Specific immunity at the ocular surface is mediated primarily through the action of IgA antibodies, which are the predominant immunoglobulin in tears of humans and experimental animals, occur almost entirely in polymeric form, and originate primarily from local production in lacrimal gland plasma cells (Chao et al., 1980; Janssen and van Bijsterveld, 1983; Sullivan and Allansmith, 1984; Peppard and Montgomery, 1987). 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 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) 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., 2002). Further, 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). S-IgA can also stimulate effector functions in eosinophils (Motegi and Kita, 1998). Antigen-IgA complexes will not ordinarily activate complement, and, 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 and aggravates the development of intestinal antitoxic protection in knockout mice (Lycke et al., 1999).

**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 major sources of the tear aqueous layer are lacrimal and accessory 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. Although complex, the inducible lacrimal secretion consists of predominantly three proteins—lysozyme, lactoferrin, and tear-specific lipocalins, each of which exhibits anti-inflammatory and antimicrobial properties (Sack et al., 2001).

Lactoferrin represents 21% of the total reflex tear protein. 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*, *E. coli*, *Proteus*), *Staphylococcus aureus*, yeast, and filamentous fungi, as well as some viruses including HIV and HCMV (Kijlstra, 1990; Sack et al., 2000, 2001).

Lysozyme represents ~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).

Tear-specific lipocalins (TSL), which represent ~25% of the reflex tear proteins, 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 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). Further, TSLs convert hydrophobic surfaces to hydrophilic ones, a property that may be useful in clearing hydrophobic foreign objects from the ocular surface and which affects tear surface tension (Gachon and Lacazette, 1998; Sack et al., 2000, 2001).

When the rate of reflex tear secretion decreases, the constitutively secreted S-IgA becomes the fourth major protein constituent. 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 defenses families. Other antimicrobial agents detected in the open eye tear fluid include β-lysin, TFF peptides, CAP-37, CAP-38, phospholipase A2, and PMN cell defensins and elastase. Also, antiproteases, various cytokines, vitronectin and neutrophil gelatinase-specific lipocalin have been detected. The reader is referred to Sack et al. (2001) for an excellent review.

Overnight eye closure is associated with an increase in S-IgA, 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; and the recruitment of PMN cells into the tear film, as well as an enhanced incidence of gram-positive bacteria in the conjunctival sac (Sack et al., 2000, 2001).

**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 a variety of 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).

**Other defense mechanisms**

Other tissues, organisms, 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 hydrodynamics 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. The normal flora depletes the tear fluid of nutrients, reacts with binding sites that might otherwise be available for pathogens, and secretes bacteriocins that make the environment less hospitable for the growth of potential pathogens (Sack et al., 2001).

**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 a number of 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 previously, conjunctiva-associated lymphoid tissue (CALT) in humans and many species functions as an antigen-sampling and, along with its draining lymph nodes, an immune inductive tissue. Also, the conjunctiva may serve as a mucosal immune effector site (Franklin and Remus, 1984; Franklin, 1989; Knop and Knop, 1996, 2000). The nasal-associated lymphoid tissue (NALT) also receives antigen after application to the conjunctival sac (Childers et al., 1996; Ridley Lathers et al., 1998). In contrast, 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 the majority of 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, intraconveal, 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 upon the form (e.g., live versus 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, its role remains unclear. Consequently, it is possible 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 this hypothesis 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). Similarly, 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, 1984b; 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).

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; McGee and Franklin, 1984; Montgomery et al., 1985; 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). IgG antibodies from serum, though, 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 both local and distant antigenic exposure, with lacrimal tissue acting as a recipient 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 levels of specific antibodies, total immunoglobulins, 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, 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 also cause modifications in the concentration of immune components in the tear film. The precise immunologic effects may depend upon the composition of lens material, the efficacy of cleaning regimens, and/or the length of wear (Mannucci et al., 1984; Vinding et al., 1987).

In contrast, such conditions as IgA deficiency, ocular surgery, keratoconjunctivitis sicca, malnutrition, or autoimmune disease may often suppress ocular mucosal immunity. Thus, 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). Similarly, autoimmune disorders such as multiple sclerosis or Sjögren’s syndrome may significantly alter or disrupt immune function in the eye. Multiple sclerosis, an autoimmune disease of possible viral origin, is associated with heightened levels of monomeric IgA and lymphocytes and reduced amounts of SC in 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 may also be due to primary infection by, and reactivation of, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes virus-6, hepatitis C, or retroviruses (Burns, 1983; Fox, 1988; Green et al., 1989; Krueger et al., 1990; Mariette et al., 1991; Fox et al., 1991; Pflugfelder et al., 1993; Mariette et al., 1993; Pepose et al., 1996). These viruses have been identified in 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 HLA-DR 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). In support of this possibility, certain viral infections in experimental animals exert a striking impact 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, recent research has demonstrated that 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), EBV may bind to specific receptors in ductal epithelium of the human lacrimal gland (Levine et al., 1990), and human immunodeficiency virus 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). However, 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, remains to be determined.

**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 and the production of glucocorticoids, and (2) the autonomic nervous system with the release of noradrenaline (Webster et al., 2002). 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 (Levite, 2000; Elenkov et al., 2000). 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). 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). Consequently, an extensive, triangular association appears to exist between the endocrine, nervous, and immune systems that acts to promote and maintain homeostasis (Befus et al., 1999; Petrovsky, 2001; Eskandari and Sternberg, 2002; Webster et al., 2002).

In the mucosal immune system, diverse hormones and neural agonists may significantly modify the (1) accumulation, proliferation, retention and/or function of IgA- and IgG-positive cells, T cells, mast cells, eosinophils, basophils, natural killer cells, polymorphonuclear leukocytes, and/or macrophages; (2) synthesis, appearance, and/or secretion of IgA and IgG antibodies, growth factors, cytokines, adhesion molecules, apoptotic factors, the expression of MHC Class II antigens, the elaboration and release of 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; Weisz-Carrington, 1987; Stead et al., 1991; 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).

With regard to the ocular mucosal immune system, endocrine (androgens, but not estrogens or stress hormones) and neural factors appear to exert a dramatic impact on immunologic expression and activity. However, although this neuroendocrine-immune interrelationship has been definitively shown in eyes of experimental animals, it has yet to be evaluated in humans. In rats, androgens elicit a marked increase in the production and secretions 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 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.

Androgen activity may also explain the pronounced, sex-related differences in the rat ocular secretory immune system. Thus, 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, wherein 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 a variety of species, including mice, hamsters, guinea pigs, rats, rabbits, and humans (Waterhouse, 1963; Cavallero, 1967; Hahn, 1969; Laurie 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; Toda et al., 1997; Rocha et al., 1997; Sullivan et al., 1998; 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) 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-1β, TNF-α, c-myb, bcl-2, and Bax) in the lacrimal gland (Wickham et al., 1996; Sullivan et al., 1997; Toda et al., 1997; Rocha et al., 1997).

In addition to androgens, the hypothalamic-pituitary axis appears to play an important role in the expression of the rat ocular secretory immune system. Disruption of this axis by hypophysectomy or extirpation of the anterior pituitary 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 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 immunooactive 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 (Russek, 1971; Nikkinen et al., 1984; Walcott, 1990; Darrt, 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’Orsio 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 et al., 1989), and systemic administration of the β-blocker, timolol, to humans, and β-blocking immunosuppression, T-cell attachment to murine lacrimal tissue (Oschger et al., 1990; Dartt, 1992; Williams et al., 1994). More recently, it has been demonstrated that VIP and the β-adrenergic receptor, isoproterenol, increase basal- and androgen-induced SC production by rat 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, carbamyl choline acutely (i.e., hours) enhances, but chronically (i.e., days) decreases, basal-, cholina 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 may involve the suppression of cAMP (Jumblatt et al., 1990) or an alteration of gene activity (Lambert et al., 1994).

Neural pathways also are of importance in the spread of herpes virus infection in the eye (Shimeld et al., 1987), and ocular viral transmission and activity may be modulated by neuropeptides (Herbert et al., 1989). Moreover, although the optic nerve does not appear to regulate the ocular secretory immune system (Sullivan et al., 1990), light does seem to control anterior chamber-associated immune deviation (Ferguson et al., 1988), herpes virus-related retinitis (Hayashi et al., 1988), and various parameters of systemic immunity (Maestroni et al., 1987).

The mucosal immune system of the eye in experimental animals may also be regulated by cytokines. For example, IL-1α, IL-1 β, and TNF-α, but not IL-6 or IFN-γ, 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, wherein TNF-α, IFN-γ, and IL-1 increase the production, surface expression, and release of SC (Kvale et al., 1988). However, the absence of IFN-γ activity on SC output by acinar cells is notable, in that this cytokine regulates SC dynamics in both intestinal (Sollid et al., 1987; Kvale et al., 1988; Nilsen et al., 1990; 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), both 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). Similarly, 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 inhibit lymphocyte binding to lacrimal gland acinar epithelium (Elfaki et al., 1994).

As a further consideration, androgens, VIP, and IL-1 all share the capacity to increase IgA production in specific tissues (Drew and Shearman, 1985; Stanisz et al., 1986; Sullivan et al., 1998), and pIgA, in turn, may heighten the monocytic output of TNF-α (Deviere et al., 1991). If analogous activity occurs in the lacrimal gland, then various neurotransmitters may control the synthesis of both 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 (pCLN) acquire antigen and appear to function as a major inductive site for eliciting tear IgA responses following 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 (s) CLN, thus following an alternate inductive pathway that bypasses the NALT and pCLN (summarized in Fig. 86.3).

It is now clear that the ocular surface and the LG function as a tightly integrated unit, linked by interconnecting innervation (Stern et al., 1998a, b). 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 86.3, conjunctival or corneal stimuli are sensed by afferent sensory neurons and the information relayed to the midbrain (lacrimatory nucleus), which also receives neural

Fig. 86.3. 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, nasal-associated lymphoid tissue, cervical lymph nodes) 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) also is received in the midbrain nucleus, a net signal is integrated and then sent through efferent nerves to the lacrimal glands. Cholinergic nerves, using acetylcholine (ACh) 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 (mAChR) 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.
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 M3 mAChR) 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 efferent neural signaling in the lacrimal gland through induction of cholinergic enzymes, which reduce expression of acetylcholine and modulate receptors (mAChR) on acinar cells and on plasma cells, thereby decreasing fluid and immunoglobulin secretion (Dannelly et al., 2001). Responses involving T lymphocyte-dependent antigens have been shown to result in production of IL-4 in lacrimal glands as well as influence cholinergic enzyme activity (Sinha et al., 2001), affecting both immune processes and lacrimal physiology. Further, neuropeptides released into lymphoid structures or inflamed tissues are known to be chemotactic for antigen presenting cells 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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