

Adaptive Immune System and the Eye: Mucosal Immunity

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Glossary

CD80 and CD86 – B7 costimulatory ligands expressed by antigen presenting cells. They interact with coreceptors CD28 and CTLA4 on T cells and are necessary, but not sufficient for T-cell activation.

MHC class II (major histocompatibility complex class II molecules) – These molecules typically acquire autoantigen epitopes in endosomes and antigen processing compartments of antigen presenting cells and present them to antigen receptors of CD4⁺ T cells.

TGF- β – Pleiotropic cytokine. One critical function in the mucosal immune system is to favor IgM-to-IgA isotype class switching; another is to promote differentiation of immature dendritic cells as regulatory antigen presenting cells. It may be mitogenic, antiproliferative, or pro-apoptotic, depending on target cell or synergistic interactions with other cytokines and growth factors.

The visual system interfaces with the external world at the epithelium of the corneal surface. The corneal epithelium is part of the convoluted yet topologically continuous surface that separates the body's *milieu intérieur* from the external world. Beyond the limbal and conjunctival epithelia, it ranges in one direction through the lacrimal excretory ducts and network of ducts to the acini of the lacrimal gland. In the other direction it ranges through the lacrimal drainage system to the oral and pharyngeal mucosae; through ducts to the acini of the salivary glands, through the airways to the alveoli of the lungs; through the mucosae of the esophagus, stomach, intestine, and colon; through ducts to the acini of the pancreas; and through ducts to the canaliculi of the liver. These moist tissues are linked topologically, via the epidermis, with the mucosal and glandular epithelia of the urinary tract, the reproductive tracts, and the mammary glands. They also are linked functionally, via the traffic of immune cells through the lymph vessels, secondary lymphoid organs, and vasculature, to comprise a physiological system, the mucosal immune system.

The metabolically active epithelial cells that comprise these surfaces perform diverse functions related to their roles in the visual, respiratory, gastrointestinal, liver, renal, and reproductive systems. However, they express several common functions. They either produce immense volumes

of fluid, for example, saliva, gastric juice, bile, pancreatic juice, and occasionally diarrhea, or produce thin, largely aqueous, but physically and chemically complex, films as homeostatic *milieus extérieurs* for themselves. They also execute innate immune functions, and, at specialized inductive and effector sites, adaptive immune functions, which protect them, their underlying stromas, and the rest of the body from particulate irritants, noxious chemicals, and infectious microbes. The central principle of the adaptive immune strategy is to use noncomplement-fixing immunoglobulins (i.e., dimeric IgA and IgG1) to prevent infection while avoiding inflammatory processes that would damage host tissues and compromise their functions. As improved sanitary systems, antibiotics, and vaccines decrease morbidity and mortality due to infection, dysfunctions of mucosal immune system tissues that result in chronic inflammatory processes join other chronic inflammatory diseases among the main categories of afflictions that burden aging populations. The chronic inflammatory mucosal immune disorders of the visual system are subsumed under the prosaic rubric, dry eye disease. Other names have been suggested, including dysfunctional tear syndrome and lacrimal keratoconjunctivitis, or, as this author would prefer, dacrykeratoconjunctivitis.

Much of the current understanding of normal mucosal immune system physiology has come from studies of the gastrointestinal and respiratory systems. The gastrointestinal system must not only prevent infection by pathogens but it must also tolerate, and to a large extent, actively host, a rich flora of commensal microbes, which benefit the organism by processing or producing nutrients that would otherwise remain inaccessible or unavailable. When the mucosal immune barrier against infection fails, conventional innate and adaptive inflammatory mechanisms mount robust responses to rescue the host organism, but these responses typically induce diarrheal fluid loss, ulcerative damage to the mucosal and stromal tissues, and malabsorption of nutrients and electrolytes. The complex relationship the mucosal immune system maintains with its microbiota is paralleled by a nuanced relationship with the foods that the gastrointestinal system processes. Nutrient carbohydrates and proteins typically are digested to monosaccharides and amino acids before being absorbed across the intestinal epithelia. Nevertheless, antigen presenting cells continuously surveille the luminal contents, and both micropinocytosis and receptor-mediated transcytosis may transfer intact nutrient macromolecules across the epithelium. Clearly, it is in the organism's interest to avoid inflammatory responses against them.

While a smaller mass and less rich diversity of commensal and infectious microbial flora challenge the ocular surface tissues, the imperative to avoid inflammatory responses while preventing infection is no less urgent than it is in the gastrointestinal system. The executive decisions largely are made by antigen presenting cells, but these decisions are based on information conveyed by paracrine mediators that are produced by parenchymal cells and mesenchymal cells, as well as by neurotransmitters and neuropeptides.

Organized Inductive Sites

New generations of mucosal antigen presenting cells, T cells, and B cells are introduced to microbes and soluble molecules in organized signaling milieus that amplify B cells with high-affinity IgM and induce them to undergo somatic hypermutation and immunoglobulin isotype class switching while continuing to retain expression of the J chain. Some authors refer to the organized inductive sites generically as mucosa-associated lymphoid tissues (MALTs) and specifically as conjunctiva-associated lymphoid tissue (CALT), eye-associated lymphoid tissue (EALT), tonsils, adenoids, bronchus-associated lymphoid tissue (BALT), and Peyer's patches and gut-associated lymphoid tissue (GALT). Other authors include both the organized inductive sites and the less organized effector sites together as MALT.

Figure 1 illustrates stereotypical features of mucosal inductive site organization. The epithelial sheet that overlays an inductive site contains specialized cells with distinctive basal convolutions enfolding superficial dendritic cells. These so-called M cells phagocytose microbes and

engulf soluble molecules at their apical surfaces, transcytose them to their basal surfaces, and release them to the underlying space. Dendritic cells in the immediate subepithelial areas again engulf the transcytosed microbes and soluble molecules, which then traffic to acidic endosomal compartments containing major histocompatibility complex class II (MHC class II) molecules and hydrolytic enzymes. Peptides that are exposed in superficial domains of the proteins being degraded have the greatest likelihood of entering the binding grooves of MHC class II molecules. Peptides that remain outside the binding grooves are exposed to further degradation. Peptide sequences that are protected from proteolysis become the dominant epitopes that the MHC class II molecules will present to $CD4^+$ T cells upon trafficking to the dendritic cells' surface membranes.

Whether or not a dendritic cell redistributes MHC class II molecules to its surface, upregulates expression of B7 costimulatory molecules, and migrates the short distance to the $CD4^+$ T-cell-rich zone may depend on signals received early in the encounter with the material it has internalized. The best understood of these signals are conveyed by lipopolysaccharides and double-stranded DNAs, which activate toll-like receptors (TLRs). The TLR activation induces a dendritic cell to downregulate chemokine receptors and homing receptors that favor retention in the subepithelial zone and to upregulate receptors that favor migration to the T-cell-rich zone. Typically, TLR activation also induces dendritic cells to upregulate surface expression of the costimulatory B7 ligands, CD80 and CD86, as they redistribute MHC class II molecule–epitope complexes to their surface membranes.

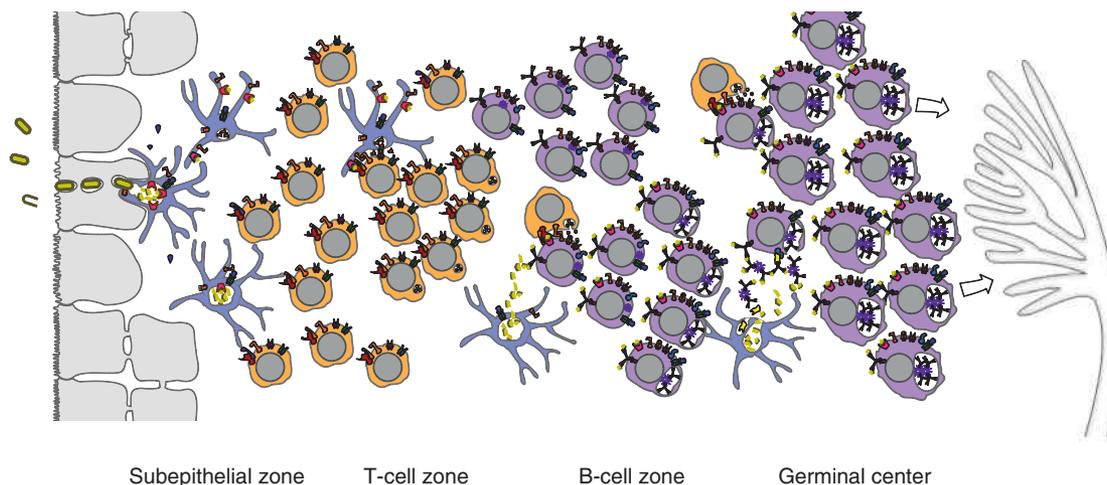


Figure 1 Stereotypical organization of mucosal immune inductive sites. After having taken up microbes or antigens transcytosed by M cells, dendritic cells may traffic directly to the B-cell zone, or they may migrate to the T-cell zone, where they activate antigen-specific $CD4^+$ cells to express T_H2 cytokines. B cells with antigen receptors of sufficient avidity internalize antigen, then use MHC class II molecules to present epitopes to activated T_H2 cells. Ongoing T_H2 activation promotes B-cell division and Ig hypermutation. In this signaling milieu, TGF- β induces IgM-to-IgA isotype class switching. In combination with B-cell growth factors, TGF- β in germinal centers promotes plasmablast proliferation and emigration via afferent lymph vessels.

While signals from engulfed microbes are decisive in determining whether the dendritic cell will undergo complete functional maturation and activation, the activated phenotype that the dendritic cell will assume is determined largely by paracrine mediators that are released by the overlying epithelium and surrounding mesenchymal cells. The signaling mediators that are known to be predominant are transforming growth factor- β (TGF- β) and interleukin (IL)-10, and they induce maturing dendritic cells to also express TGF- β and IL-10. An additional population of dendritic cells are distinguished by the absence of MHC class II molecule expression and expression of chemokine and homing signal receptors that lead them to bypass the T-cell-rich regions and enter B-cell-rich zones, where there they will release the material they had internalized.

Engagement of a naive CD4⁺ T cell's antigen receptors by MHC class II molecule–epitope complexes generates the primary signal necessary, but not sufficient, for activation. Simultaneous engagement of CTLA-4 or CD28 at the T-cell surface by CD80 or CD86 at the dendritic cell surface provides the second signal essential for promoting T-cell activation and differentiation. However, the functional phenotype the activated CD4⁺ T-cell expresses is determined by paracrine mediators in the immediate signaling milieu. These are secreted by dendritic cells, epithelial cells, and mesenchymal cells. They induce CD4⁺ T cells to differentiate as T_{H2} cells and to change their panel of chemokine receptors and homing receptors to favor migration from the T-cell-rich zones and into the B-cell-rich zone.

When molecules that dendritic cells have released encounter B cells with surface IgM antigen receptors that bind them with high enough affinity, they deliver a primary activation signal, which induces the B cell to endocytose the IgM–antigen complex to antigen-processing compartments and to begin expressing MHC class II molecules. Thus, CD4⁺ T cells arriving from the interfollicular zone will be presented with dominant epitopes that maintain them in their activated state. They continue secreting the T_{H2} cytokines needed to induce somatic hypermutation of B-cell immunoglobulin genes and promote selection of B-cell clones with increasing affinity for the determinant. The signaling milieu within some of the organized inductive sites, notably Peyer's patches, selectively induce IgM-to-IgA class switch recombination. The milieu in the inductive sites in the tonsils, adenoids, and airways may induce either IgM-to-IgA or IgM-to-IgG1 class switch recombination. In cases of IgA deficiency, the numbers of IgG1⁺ cells and IgM cells may increase in compensation. Whether induced to express IgA or IgM, the activated B cells continue to express J chain. The IgA⁺ B cells will express dimeric IgA (dIgA), while IgG1 B cells will express apparently irrelevant J chain.

The activated B-cell blasts amplify in germinal centers, and they alter their panel of chemokine receptors and

homing receptors, so that they are induced to leave the inductive sites via lymph vessels, enter the circulation via the thoracic duct, and enter the mucosal immune effector sites. The IgA⁺ B cells expressing CCR10, the receptor for CCL28, traffic to the lamina propria of the oral cavity, lower airways, and colon. The IgA⁺ B cells expressing CCR9, the receptor for CCL25, traffic to the trachea, stomach, intestine, salivary glands, and mammary gland. The IgG1⁺ B cells expressing CXCR4, the receptor for CXCL12, traffic to the bone marrow. In each setting, the plasmablasts will take residence and mature to become long-lived memory cells or plasmacytes.

Effector Sites

Specialized Niches

Stereotypical features of the mucosal immune effector site are illustrated in the upper panel of **Figure 2**. Like IgG⁺ plasmablasts entering the bone marrow, the dIgA⁺ plasmablasts that arrive in the mucosal effector sites receive signals that induce them to mature into plasmacytes. One of the critical mediators of maturation signaling at the mucosal effector sites is TGF- β . A mature plasmacyte's ongoing survival depends on the constant presence of additional signals to suppress the intrinsic apoptotic program. The candidate mediators of the survival signals include IL-6, B-cell activating factor (BAFF), a proliferation-inducing ligand (APRIL), and, perhaps, prolactin. In the rabbit lacrimal gland, which has been studied in some detail, epithelial expression of paracrine mediators is compartmentalized according to the epithelial histoarchitectural plan and vascular organization. Venues, the vascular elements that plasmablasts cross to enter the stromal space, tend to follow courses that parallel interlobular ducts. Epithelial cells of the interlobular ducts express TGF- β and prolactin at much higher levels than epithelial cells in the acini, and it appears they secrete these mediators both apically (i.e., into the fluid forming within the duct lumen) by way of their regulated exocrine secretory apparatus for proteins, and also basally, through either a constitutive paracrine secretory apparatus or a parallel paracrine apparatus that can be induced under certain circumstances. While TGF- β , as noted, induces dIgA⁺ plasmablast-to-plasmacyte differentiation, it may not be conducive to the plasmacytes' ongoing survival. It appears that TGF- β signaling may be concentrated in the stromal spaces surrounding the venues and interlobular ducts. Preliminary findings in the author's laboratory suggest that transcripts for the extracellular matrix proteoglycan, decorin, are two orders of magnitude more abundant than TGF- β transcripts in lacrimal gland epithelial cells. Because decorin binds to the extracellular matrix and also binds the latent TGF- β , it may create a diffusion barrier that keeps latent TGF- β

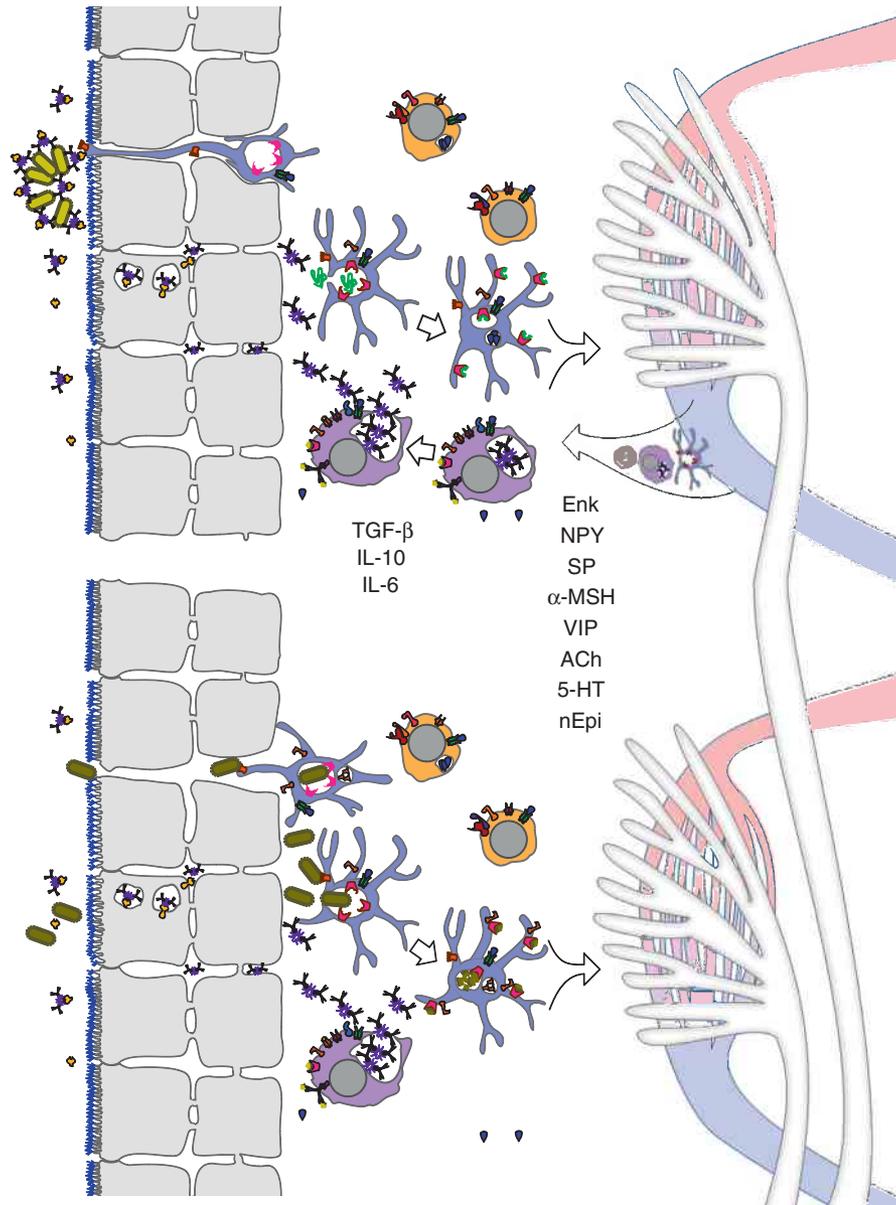


Figure 2 Normal (upper panel) and infected (lower panel) mucosal immune effector sites. IgA⁺ J chain⁺ plasmablasts, immature dendritic cells, and T cells enter the lamina propria of the conjunctiva and drainage system, stromal space of the lacrimal gland, and other effector sites from venules. Paracrine mediators induce plasmablasts to undergo terminal differentiation, then support their survival as plasmacytes. Of these mediators, TGF-β, IL-10, and IL-6 are provided, at least in part, by epithelial and stromal cells. Sensory, parasympathetic, and sympathetic nerve endings provide neurotransmitters and neuropeptides that may also influence plasmablasts, plasmacytes, dendritic cells, and lymphocytes. The normal signaling milieu induces dendritic cells that have taken up soluble proteins and cellular debris to mature as regulatory antigen presenting cells, which exit via afferent lymph vessels and induce regulatory T cells in the lymph nodes. The TLR activation by microbes that have evaded the immunospecific sIgA barrier induces dendritic cells to mature as immunoactivating antigen presenting cells that will elicit IgG responses in the lymph nodes.

concentrated in the periductal stroma. In contrast, prolactin may be free to equilibrate through the interstitial fluid, diffusing to plasmablasts throughout the gland's stromal spaces. Preliminary studies suggest that acinar epithelial cells may be able to express IL-6. In contrast, mRNAs for APRIL and BAFF appear substantially more abundant in whole gland extracts than in *ex vivo* acinar

cells. If substantiated, this finding would imply that APRIL and BAFF are expressed by infiltrating lymphocytes, but it cannot exclude significant expression by ductal epithelial cells.

The information so far available about the cytophysiological mechanisms that secrete paracrine mediators to the stroma has come from immunohistochemical studies

of TGF- β , epidermal growth factor (EGF), fibroblast growth factor (FGF), and prolactin localizations in rabbit lacrimal gland and studies of the intracellular traffic of prolactin in *ex vivo* acinar cells from rabbit lacrimal gland. Under normal circumstances, the paracrine mediators are localized primarily in the apical cytoplasm, consistent with secretion into the duct lumen via the regulated exocrine secretory apparatus. Consistent with this inference, pilocarpine-induced lacrimal gland fluid contains high concentrations of TGF- β and prolactin. Two-color confocal immunofluorescence microscopy of the *ex vivo* model indicates that prolactin colocalizes with rab4, rab5, and rab11, which are effectors of traffic to and from endosomes, and electron microscopic-immunogold studies indicate that prolactin also is localized within mature secretory vesicles. These findings suggest that lacrimal epithelial cells may maintain two pools of the paracrine mediators they secrete: a large, often static, pool in the regulated exocrine secretory apparatus, and a small, but high throughput, pool in the paracrine apparatus.

Transfer of Immunoglobulins to the *Milieu Extérieur*

pIgR and dIgA

Several prominent aspects of lacrimal cytophysiology appear to reflect adaptations to the roles the epithelium plays in the mucosal immune system: maintaining the underlying stromal space as a niche for dIgA-secreting plasmacytes and then transferring dIgA from the stromal space to the fluid within the lumen of the acinus-duct system. The fundamental principles of the transcytotic mechanism for dIgA secretion were elucidated in studies of madin-darby canine kidney (MDCK) cells, derived from a canine kidney, which form continuous epithelial monolayers when cultured on microporous substrata. Renal tubular epithelial cells do not normally secrete IgA, but when MDCK cells are stably transduced to express the polymeric immunoglobulin receptor (pIgR), they gain the ability to internalize dIgA from their basal medium, which corresponds to the interstitial fluid, and secrete sIgA into their apical medium, which corresponds to the luminal fluid of an exocrine gland or the surface fluid of a mucosal sheet. **Figure 3** illustrates the transcytotic apparatus as it is thought to function in conjunctival epithelial cells. The pIgR makes its way from the biosynthetic apparatus, that is, the endoplasmic reticulum and Golgi complex, through the trans-Golgi network (TGN) and endosomes, to the basal-lateral plasma membranes, hitchhiking in transport vesicles at each step. The pIgR may or may not bind the J chain and associated immunoglobulin while its ligand-binding domain is exposed at the basal-lateral membrane. In either case, it is internalized in an endocytotic transport vesicle that will traffic to the

early endosome. Another transport vesicle will traffic pIgR and pIgR-dIgA complex to the recycling endosome, and yet another will traffic pIgR and pIgR-dIgA complex to the apical plasma membrane. Either during its transit through the recycling endosome, or upon arriving at the apical plasma membrane, the pIgR will encounter a protease that cleaves the extracytoplasmic, dIgA-binding domain, referred to as secretory component (SC), from the membrane-spanning domain. Thus, the cell releases both free SC and SC-dIgA complexes, that is, secretory IgA (sIgA), into the *milieu extérieur*. Consistent with the topological constraints that preclude traffic of transport vesicles between adjoining cells, expression of pIgR is concentrated in the apical-most layer of epithelial cells in the conjunctiva.

Acute Regulation of pIgR Traffic

The traffic of pIgR through lacrimal gland epithelial cells appears to be somewhat more complex than described in the MDCK cell paradigm. First, it appears that pIgR might cycle repeatedly to the basal-lateral plasma membrane from any compartment of the transcytotic apparatus, while free SC is preferentially trafficked from the recycling endosome to the apical plasma membrane. Second, some of the pIgR traffic from the TGN to the immature secretory vesicle, rather than to the transcytotic apparatus; SC derived from these pIgR remains in mature secretory vesicles until released into the lumen along with the classical secretory proteins. Interestingly, many of the classic lacrimal secretory proteins, such as β -hexosaminidase, lysozyme, and lactoperoxidase, are innate immune effector molecules. Free SC appears to perform important functions in the ocular surface fluid film, and the ability to sequester a portion of pIgR away from the transcytotic apparatus ensures that some free SCs always will be secreted, despite the large mass of dIgA that normally is present in the stromal space.

A considerable volume of membrane traffic flows through the lacrimal acinar cell's transcytotic apparatus. The micropinocytosis associated with endocytotic internalization of transport vesicles from the basal-lateral and apical surface membranes carries fluid phase markers into the cells, and such markers rapidly equilibrate throughout the aqueous phase within the lumina of the early endosome, recycling endosome, and TGN, as well as the late endosome, prelysosome, and lysosome. If *ex vivo* acinar cell models are acutely stimulated with the muscarinic acetylcholine receptor agonist, carbamylcholine (carbachol, CCh), they increase the rates at which they endocytose and exocytose fluid phase markers. If the CCh concentration is increased from 10 μ M, which maximally accelerates fluid phase endocytosis but half-maximally accelerates protein secretion, to 100 μ M, a concentration that maximally accelerates protein secretion, fluid phase endocytosis continues at the increased rate, but

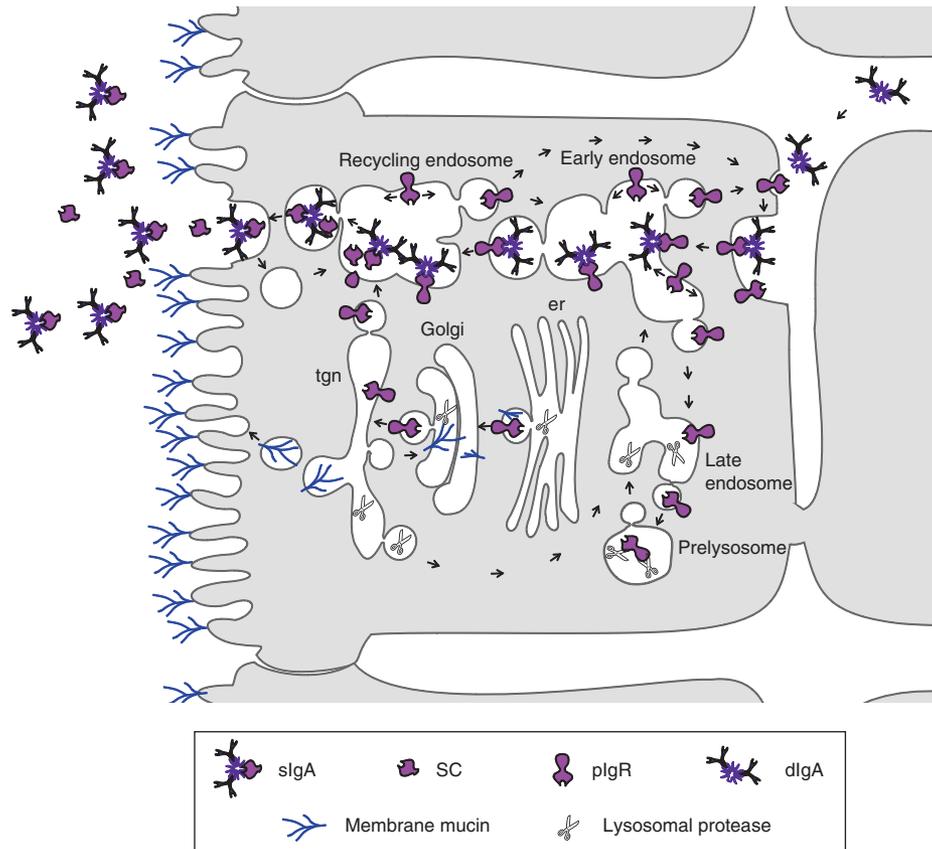


Figure 3 Transcytotic traffic of sIgA to the *milieu extérieur*. The apical-most layer of epithelial cells in stratified tissues, like the epithelial cells of lacrimal acini and ducts, express pIgR. At the basal-lateral surface membrane pIgR mediates endocytosis of dIgA, which it then chaperones through the early endosome and apical recycling endosome. Either within the apical recycling endosome or at the apical plasma membrane, the pIgR is cleaved by protease to release either free SC or dIgA-SC complex, that is, sIgA. In lacrimal gland epithelial cells, pIgR may cycle repeatedly through the TGN and transcytotic apparatus; it may enter immature secretory vesicles (not shown), where free SC is released and stored for subsequent secretion in response to secretagogue stimulation, or it may traffic through the late endosome, which is a gateway to the prelysosome and autophagic-lysosomal apparatus. The author proposes that the traffic of transport vesicles returning from the prelysosome and late endosome to the early endosome accounts for the constitutive release of an unusually heavy burden of autoantigens to the stromal space.

the volume of space that the fluid can reach decreases. If a marker is allowed to equilibrate through the fluid phases of the network of endomembrane compartments under resting conditions, subsequent acute stimulation with 100 μ M CCh accelerates its release, but release then stops with a substantial portion of the marker remaining entrapped within the cell. These findings suggest that when the cell is maximally stimulated with CCh, it imposes a blockade of bidirectional traffic between proximal and distal compartments of the endocytotic pathway. Other studies indicate that the blockade affects traffic to the late endosome from both the early endosome and the TGN. A possible cytophysiological rationale for this phenomenon is suggested by preliminary studies of the kinetics of CCh-induced SC secretion. The CCh acutely induces a burst of secretory vesicle exocytosis, which releases SC along with the other secretory proteins. Secretory vesicle exocytosis is complete within 10 min. However, the cells continue to release SC at an increased rate for at least 60 min, while

their total content of pIgR plus SC appears to remain unaltered. These phenomena suggest that the cell blockades traffic to the late endosome in order to divert an increased proportion of its newly synthesized pIgR from the degradative apparatus to the transcytotic apparatus.

A Mechanism That Constitutively Secretes Autoantigens to the Stroma

A consequence of the strategy of directing a large volume of transport vesicle traffic from the early endosome to the late endosome and prelysosome under nonstimulated conditions is that the reciprocal traffic of transport vesicles constitutively secretes lysosomal hydrolases and potential autoantigens that, in other cells, would remain in the autophagic-lysosomal apparatus and be degraded. Moreover, when traffic to the late endosome is blocked, the lysosomal hydrolases reflux into the compartments which remain accessible (i.e., the TGN), immature

secretory vesicle, early endosome, and recycling endosome. Of particular interest, at least some of the lysosomal proteases are catalytically active and may process other proteins that have accumulated with them in the same compartments. This phenomenon might lead to the degradation of dominant autoantigen epitopes and lead to the eventual presentation of epitopes that under normal circumstances are degraded.

Fc γ Rn and IgG1

While the plasmacytes that produce dIgA reside in the stromal spaces of exocrine glands and the lamina propria of mucosal sheets, the plasmacytes that produce IgG1 typically reside in the bone marrow, and IgG1 must travel through the circulation to reach the epithelia that will secrete it. The same subcellular apparatus that transports SC and pIgR–dIgA complexes through epithelial cells likely also mediates the secretion of IgG1. However, IgG1 does not associate with J chain, and its traffic is mediated not by pIgR but by the neonatal Fc γ receptor, Fc γ Rn. The association between IgG1 and Fc γ Rn is regulated by pH, such that binding affinity is highest in relatively acidic endosomal compartments and lower at the pH of the interstitial fluid. In the tissues where it has been studied, the IgG1–Fc γ Rn complex tends to bypass the late endosome in favor of the early endosome and recycling endosome. Because dissociation of IgG1 from Fc γ Rn does not require proteolytic processing, Fc γ Rn can mediate multiple cycles of IgG1 absorption as well as secretion. The Fc γ Rn can also mediate absorption and secretion of IgG1-immune complexes, in some cases secreting opsonized microbes and immune complexes and in others absorbing them in a physical state that minimizes the risk of infection but perpetuates T-cell and B-cell responses. The extent to which Fc γ Rn might be expressed in the lacrimal glands and drainage system has not been investigated; recently, however, it has been found to be present in epithelial cells of rat conjunctiva.

Mucosal Tolerance and Response to Infection

Commensal microbes in the gut are coated with sIgA, which normally prevents them from entering the epithelial lining. Notably, dendritic cells as well as dIgA-secreting plasmacytes populate the mucosal effector sites. They are present within the lamina propria and the epithelia and may extend processes that interdigitate between adjoining cells to surveil the *milieu extérieur*. As in the organized inductive sites, immature dendritic cells are endocytotically active, and under normal circumstances the material they internalize consists of soluble molecules and cellular debris.

The robustness of the phenomenon of oral tolerance suggests that the TGF- β - and IL-10-rich milieu directs them to mature as regulatory antigen presenting cells, which, when they arrive in lymph nodes, induce food antigen- and, presumably, autoantigen-specific CD4⁺ T cells to mature as T_H3 and T_R1 regulatory cells. The regulatory cells might function in both the effector sites and the lymph nodes to prevent inflammatory mediators or activated effect T cells from redirecting dendritic cells toward expression of immunoactivating phenotypes.

As illustrated in the lower panel of **Figure 2**, TLR on immature dendritic cells in the epithelium or lamina propria recognizes microbes that have evaded the immunospecific sIgA barrier, and TLR activation induces phagocytosis, redistribution of MHC class II molecules to the dendritic cell surface, and upregulation of surface CD80 and CD86. Certain microbes induce maturing dendritic cells to remain in the lamina propria and release antigen directly to B1 cells, stimulating activation independently of T-cell help. Typically, however, dendritic cells are activated to switch chemokine receptor and homing receptor expression to favor emigration via afferent lymph vessels. In the lymph nodes, they will induce activation of naive, antigen-specific CD4⁺ T cells as T_H2 cells and generation of IgG-producing B cells.

Implications for Ocular Surface Pathophysiology

Contemporary paradigms hold that dry eye disease results from insufficiency of the ocular surface fluid film. Such might be the consequence of impaired lacrimal gland fluid production, excessive evaporation of water from the ocular surface fluid due to deficient production of lipids in the Meibomian glands, and excessive breakup of the fluid film due to deficiencies of the normally hydrophilic substratum provided by the apical surfaces of corneal and conjunctival epithelial cells. There is a general consensus that, whatever the etiology, the principal feature of pathophysiological state is inflammation of the ocular surface tissues. Inflammatory processes plausibly account for much of the cytopathology that occurs within the lacrimal gland and leads to quiescence of impairment of its exocrine functions. This seems to be the case, not only in Sjögren's syndrome, but also in graft-versus-host disease, sarcoidosis, Wegener's granulomatosis, and diffuse infiltrative lymphocytosis syndrome associated with HIV infection. A histopathological syndrome distinct from the familiar diagnoses and described primarily through postmortem studies is characterized by lymphocytic infiltration, acinar atrophy, ductal dilatation, and periductal fibrosis. Its underlying pathophysiological mechanisms have not been studied, although they appear not to involve production of autoantibodies.

The author suggests that these inflammatory processes normally are prevented by the same strategy that prevents immune responses to food antigens, soluble autoantigens, and cellular debris. There may be particular challenges to maintaining immunoregulation in the lacrimal glands, where vigorous traffic through the transcytotic apparatus releases an exceptionally heavy burden of potential autoantigens into the stromal space, and in the ocular surface tissues, where environmental stresses may induce release of inflammatory mediators that abrogate the local signaling milieu's ability to generate regulatory antigen presenting cells. Additional challenges may result from the epithelia's dependence on systemic hormones to maintain expression of the local signaling milieu.

See also: Adaptive Immune System and the Eye: T Cell-Mediated Immunity; Conjunctiva Immune Surveillance; Defense Mechanisms of Tears and Ocular Surface; Lacrimal Gland Overview; Tear Film; Tear Film Overview.

Further Reading

- Brandtzaeg, P. and Johansen, F.-E. (2005). Mucosal B cells: Phenotypic characteristics, transcriptional regulation, and homing properties. *Immunological Reviews* 206: 32–63.
- Cain, C. and Phillips, T. E. (2008). Developmental changes in conjunctiva-associated lymphoid tissue of the rabbit. *Investigative Ophthalmology and Visual Science* 49: 644–649.
- Evans, E., Zhang, W., Jerdeva, G., et al. (2008). Direct interaction between Rab3D and the polymeric immunoglobulin receptor and trafficking through regulated secretory vesicles in lacrimal gland acinar cells. *American Journal of Physiology. Cell Physiology* 294: C662–C674.
- Franklin, R. M, Kenyon, K. R., and Tomasi, T. B. (1973). Immunohistologic studies of human lacrimal gland: Localization of immunoglobulins, secretory component and lactoferrin. *Journal of Immunology* 110: 984–992.
- Kaetzel, C. S. (2005). The polymeric immunoglobulin receptor: Bridging innate and adaptive immune responses at mucosal surfaces. *Immunological Reviews* 206: 83–99.
- Kim, H., Fariss, R. N., Zhang, C., et al. (2008). Mapping of the neonatal Fc receptor in the rodent eye. *Investigative Ophthalmology and Visual Science* 49: 2025–2029.
- Knop, E., Knop, N., and Claus, P. (2008). Local production of secretory IgA in the eye-associated lymphoid tissue (EALT) of the normal human ocular surface. *Investigative Ophthalmology and Visual Science* 49: 2322–2329.
- Macpherson, A. J., McCoy, K. D., Johansen, F.-E., and Brandtzaeg, P. (2008). The immune geography of IgA induction and function. *Mucosal Immunology* 1: 11–22.
- Meagher, C. K., Liu, H., Moore, C. P., and Phillips, T. E. (2005). Conjunctival M cells selectively bind and translocate Maackia amurensis leukoagglutinin. *Experimental Eye Research* 80: 545–553.
- Mircheff, A. K., Wang, Y., de Saint Jean, M., Ding, C., and Schechter, J. E. (2007). Lacrimal epithelium mediates hormonal influences on APC and lymphocyte cycles in the ocular surface system. In: Zierhut, M., Rammensee, H. G., and Streilein, J. W. (eds.) *Antigen Presenting Cells and the Eye*, pp. 93–119. New York: Informa.
- Rose, C. M., Qian, L., Hakim, L., et al. (2005). Accumulation of catalytically active proteases in lacrimal gland acinar cell endosomes during chronic *ex vivo* muscarinic receptor stimulation. *Scandinavian Journal of Immunology* 61: 36–50.
- Seder, R. A., Marth, T., Sieve, M. C., et al. (1998). Factors involved in the differentiation of TGF- β -producing cells from naive CD4+ T cells: IL-4 and IFN- γ have opposing effects, while TGF- β positively regulates its own production. *Journal of Immunology* 160: 5719–5728.
- Spiekermann, G. M., Finn, P. W., Ward, E. S., et al. (2002). Receptor-mediated immunoglobulin G transport across mucosal barriers in adult life: Functional expression of FcRn in the mammalian lung. *Journal of Experimental Medicine* 196: 303–310.
- Wang, Y., Chiu, C. T., Nakamura, T., et al. (2007). Traffic of endogenous, over-expressed, and endocytosed prolactin in rabbit lacrimal acinar cells. *Experimental Eye Research* 85: 749–761.
- Weiner, H. L. (2001). Induction and mechanism of action of transforming growth factor- β -secreting Th3 regulatory cells. *Immunological Reviews* 182: 207–214.