Corneal Antigen-Presenting Cells: Diversity, Plasticity, and Disguise
The Cogan Lecture

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The study of antigen-presenting cells (APCs) is important for all immune-mediated disorders because these cells are not only the “sentinels” of the immune system for detection of foreign antigens, but they also play a critical role in tolerance induction to both self- and foreign antigens.1-4 In addition to their role in immune surveillance and induction of antigen-specific immune reactivity and tolerance, APCs can also serve an important role in innate immunity due to their capacity to respond acutely to inflammatory insults or “danger” signals in peripheral tissues.5-7

APCs can be divided into two functional groups: "professional” and “nonprofessional” APC. Professional APCs are thus called because they generally have a high constitutive expression of major histocompatibility complex (MHC) class II antigen, as well as costimulatory molecules, and hence are capable of efficient provision of both signals for T-cell priming.2,8 Examples of professional APCs include dendritic cells (DCs), macrophages, B cells, and epithelial Langerhans cells (LCs).9,10 In contrast to professional APCs, nonprofessional APCs have a low T-cell stimulatory capacity because their constitutive expression of MHC class II antigen and costimulatory molecules is low; however, under certain circumstances (as may occur in inflammation) these cells may also provide requisite signals for T-cell priming. Examples of nonprofessional APCs include vascular endothelial and certain mesenchymal cells. The most potent APCs in most tissues are DCs and LCs. Indeed, these cells are also known to serve as the professional APCs of the cornea and ocular surface.11-16 Their activation and recruitment to the cornea has been associated with loss of “immune privilege” in the anterior segment,17 exacerbation of herpetic18,19 and Pseudomonas20 keratitis, and amplification of transplant immunity.15,21-24

The focus of our laboratory has been on studying the molecular factors that mobilize corneal APCs. Specifically, we have been interested in determining the (1) adhesion factors at the level of the limbal vascular endothelium that are required for leukocyte recruitment from the intravascular compartment into the tissue matrix, (2) chemotactic signals that are critical for recruiting limbal APCs into the cornea, (3) phenotypic and functional alterations to APCs associated with their maturation in the inflamed corneal microenvironment, (4) molecular factors that allow for mobilization and egress of mature APCs into lymphatics, and (5) critical costimulatory factors required for T-cell priming in lymphoid organs. Most of our studies to date addressing the above questions have exploited the orthotopic corneal transplant model in the mouse. This model, while technically challenging, offers distinct advantages for the study of corneal immunobiology. First, to the extent that they have been studied, the cellular and molecular mechanisms of murine corneal allotransplant rejection largely resemble those of the human. Second, because of its clarity, the cornea is a perfect tissue for directly observing immunoinflammatory responses without the need to sacrifice the eye or the animal. Third, because of its easy accessibility, the cornea is an optimal tissue for atraumatic local immune modulation. Fourth, known immunogenetic differences between inbred strains of mice make this corneal model an optimal method for delineating the contribution of donor versus host-derived cells to the generation of the immune response to corneal antigens. Finally, and importantly, the study of corneal graft (by far the most common form of transplantation) immunology remains a priority because of the propensity of corneal grafts to be rejected when they are grafted onto inflamed host beds.25-27

Recombinant of Limbal APCs into the Cornea

It has been known for a long time that the limbus, the area between the vascularized conjunctiva and avascular cornea, has a significant resident population of MHC class II+ LCs, which when stimulated can be recruited into the cornea.15,21,28-33 What are the molecular factors that mediate the recruitment of these cells? It is well known that in general the migration of leukocytic populations to peripheral tissues requires the concerted activity of adhesion and chemotactic factors.34 Cell adhesion molecules (CAMs) regulate both cell-cell and cell-matrix interactions. A classic example of the former is the interaction between leukocytes and vascular endothelial cells (VECs) that allow leukocytes to adhere and roll on the VECs before their transendothelial migration from the intravascular compartment into the tissue matrix.35-37 The transcriptional expression of many CAMs is under the regulation of signal-transduction pathways, such as NF-kB, that are in turn activated by proinflammatory cytokines and microbial products such as lipopolysaccharide (LPS).38 An early clue to the specific molecular mechanisms that initiate APC recruitment into the cornea was the identification of interleukin (IL)-1 as a principal proinflammatory cytokine that is secreted by the cornea itself at high levels within hours of inflammatory or immunogenic insult.34 The function of IL-1 requires ligation of IL-1 receptor I by agonistic ligands IL-1α and IL-1β; conversely, the high-affinity binding of the receptor by IL-1 receptor antagonist (IL-1Ra) not only fails to generate signaling, but also competitively prevents binding of the receptor by the agonistic ligands.39-42 We have shown that the early expression of IL-1 by the inflamed cornea leads to profound upregulation in the expression of intercellular adhesion molecule (ICAM)-1 by the limbal vascular endothelium, which pre-

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ceeds the recruitment of leukocytes to the peripheral cornea. 44 The critical role of ICAM-1 in mediating the early leukocytic recruitment is underscored by our studies of ICAM-1 knockout animals and by the topical application of IL-1Ra (which leads to near-total downmodulation of ICAM-1 expression). In both settings, extravasation of innate immune cells (including macrophages and neutrophils) is dramatically suppressed. 11,42 In the corneal transplantation model, the recruitment of limbal (i.e., host-derived) LCs into the allografts is likewise suppressed by 70% to 90% as a result of IL-1 blockade with IL-1Ra. 156 However, because the peak recruitment of LC/DC elements into the cornea is preceded by infiltration of neutrophils (and to a lesser extent macrophages), our overall paradigm has emphasized the early role of these innate immune cells, in large part in response to ICAM-1 overexpression, as a critical facet of subsequent infiltrating waves of APCs into the cornea. 44 In turn, the functional relevance of APC recruitment into the cornea prior to generation of any demonstrable T-cell-mediated immune reactivity is reflected in the profound effect that suppression of APc infiltration into the cornea has on allograft survival. For example, blockade of limbal LC infiltration into grafts effected by local IL-1 suppression is associated with a profound suppression of both allospecific delayed-type hypersensitivity (DTH) and frequency of allorecognition. 45,45 The role of IL-1 in mobilizing corneal APCs is far from absolute. Indeed, we have been impressed by the fact that local IL-1 suppression has a more limited effect on modulating generation of immunity in the setting of “high-risk” allografts (i.e., performed in presensitized hosts or those with inflamed recipient beds) compared with its immunomodulatory role in “low-risk” grafts performed onto uninflamed host beds. 45 Initial clues to the involvement of another proinflammatory cytokine, tumor necrosis factor (TNF-α), in mobilizing limbal LCs came when we determined that many limbal LCs do not express IL-1R and IL-1 has a very limited capacity in recruiting LCs in TNF-knockout hosts, whereas TNF-α can mediate LC recruitment into the cornea even in IL-1RI knockout mice, 46 thereby establishing TNF as a critical mediator of the induction phase of corneal immunity. 44,47,48

Given that TNF-α is a highly pleiotropic cytokine, how does it mediate corneal immunity? Insight into this area came through our studies focusing on chemokine immunobiology in the context of corneal transplantation. Chemokines, or chemotactic cytokines, are low-molecular-weight cytokines that act as the “traffic cops” of the immune cells by providing directional information (through a gradient) to infiltrating cells in tissues. 53 Most limbal LCs express CCR5, a receptor in the CD45 or β group of chemokines, whose role in mediating recruitment of limbal LCs into the cornea is reflected by the fact that CCR5-knockout animals demonstrate a significant blunting in their capacity to mobilize LCs in response to corneal injury (Vora SR, et al. IOVS 2001;42:ARVO Abstract 2538). Similarly, we have shown that local suppression of TNF-α signaling (through the use of soluble TNFRI) can significantly suppress limbal LC recruitment into the cornea by effective suppression of gene transcription for regulated on activation normal T-cell expressed and secreted (RANTES) and macrophage inflammatory protein (MIP)-1β, 48 two principal ligands of CCR5. 52

In conclusion, IL-1 and TNF-α can act in concert to recruit APCs from the limbus into the cornea by mediating the expression of cell adhesion factors (e.g., ICAM-1 and chemokines), in particular those that mediate signaling through the CCR5 receptor. Indeed, the maximally effective immunomodulatory strategy for blocking APC ingress into the cornea, as far as we know, is the combination of IL-1 and TNF-α blockade (Vora SR, et al. IOVS 2001;42:ARVO Abstract 2538).

Corneal APCs: A Heterogeneous Cast of Cells

Until recently, it was thought that the normal cornea is essentially devoid of all bone-marrow–derived cellular, including APC, elements. 15,16,20,30 Indeed, this putative unique feature of the cornea was maintained to be central to the immune privilege enjoyed by the cornea and ocular anterior segment. 5,23,53 This tenet was refuted recently with the definitive demonstration that the cornea in fact possesses its own resident bone-marrow–derived CCR5+ population. First, our laboratory identified CCR1+CCR12+CD11b−LCs in the epithelium (including central regions) of the normal cornea that bear classic ultrastructural features of epidermal LCs. 11,13 Second, both our and Hendricks’ laboratories have recently identified CD45+CD11b+CD11c−monocytic cells in the corneal stroma. 12,54 Third, in the very anterior portions of the corneal stroma, we have also identified a population of myeloid (CD8α+) monocytic (CD11b+) CD11c+DCs 14 that demonstrate a distinct ultrastructure compared with the monocytic CD11c+ cells present in the more posterior portions of the cornea. Finally, a fourth population of CD14+ undifferentiated or precursor-type cells have been identified throughout the corneal stroma, most of which fail to express classic monocytic or DC surface markers. 11,12 As discussed earlier, for APCs to prime T cells, they must present antigen in the groove of MHC class II, along with requisite costimulatory signaling. However, what is unique to the bone-marrow–derived cells of the central cornea is that they are universally both MHC class II– and costimulatory-factor (CD40, CD80, CD86)–negative. 12 Although highly immature APC populations have been identified in lymphoid organs and blood, 2,55,56 no other tissue has been reported to be replete with universally MHC class II–negative CD45+ cells. It is the discordance between the cell surface expression of classic APC markers by these corneal cells and by similar lymphoreticular cells in other tissues that accounts for the “disguising” characteristic of the corneal bone-marrow–derived cells. Indeed, in retrospect, the failure to detect constitutively MHC class II–expressing resident cells in the corneas was the principal reason for the (inaccurate) conclusion that the cornea is devoid of resident lymphoreticular cells. 50

Functional Aspects of Corneal Bone-Marrow–Derived Cells

Although the centrally located CD45+ cells of the cornea do not express the full complement of classic APC cell surface markers, approximately half of the CD45+ cells in the corneal periphery and limbus do. 11,57 At least two important questions arise: Does the phenotype of the bone-marrow–derived cells (i.e., those that normally reside in the cornea and those that are recruited there from the limbus) in the cornea change in inflammation? And, are these bone-marrow–derived cells actually capable of functionally serving as APCs for corneal antigens? As for the first question, our experimental data suggest that in addition to the recruitment of a large number of cells from the limbus into the cornea (through the molecular mechanisms detailed earlier), there is also a profound upregulation in the expression of MHC class II and costimulatory molecules (CD80/CD86) by resident corneal (as well as limbal) bone-marrow–derived cells in response to inflammation. 11,13,57 These changes are experimentally very nicely reflected after corneal allotransplantation, because one can differentiate the limbal host-derived cells from the (donor) graft-residing CD45+ cells based on their expression of different MHC molecules. We have shown that, although the normal corneal graft tissue remains incapable of significant MHC class II expression as late as 12 hours after transplantation, by 24
hours there is significant expression of donor-type MHC class II—in particular near the graft–host junction, which coincides with the area of most significant inflammation in transplantation.\textsuperscript{3,5} Hence, in the aggregate, at least from the standpoint of cell surface markers, corneal bone-marrow–derived cells can phenotypically mature into cells that express “classic” APC markers.

To demonstrate their functional capacity as APCs, we used transgenic green fluorescent protein (GFP) donor grafts transplanted into wild-type (non-GFP–expressing) hosts. Our data clearly show that graft-derived cells can be detected leaving the transplant and migrating centrifugally into the recipient rim, and eventually localizing into the ipsilateral draining lymph nodes of the host—strongly suggesting that these cornea-derived cells can act as “passenger leukocytes” in the context of transplantation immunology.\textsuperscript{14} Initial clues to the functional relevance of this traffic came when we demonstrated that disruption of the eye–lymph node axis, through surgical cervical lymphadenectomy, leads to both complete abrogation of host allosensitization and universal and indefinite allograft survival.\textsuperscript{55,56} Indeed, these data demonstrate that the functional presence of the eye–lymph node axis (immunization) can be directly juxtaposed with the occlusoplastic axis (tolerance induction).\textsuperscript{58,59}

From a conceptual standpoint, however, both host and donor-derived APCs should be able to gain access to the draining lymph node; hence, the lymphadenectomy data referenced earlier did not definitely relate the induction of immunity in lymph nodes to the donor (graft-derived) APCs, per se. It is important at this juncture to review briefly and distinguish “direct” from “indirect” allosensitization in transplantation, as these concepts have a considerable impact on our discussion. In direct sensitization, graft-borne passenger leukocytes serve as antigen-presenting alloantigen(s) in the context of donor-type MHC class II to naive host T cells.\textsuperscript{60} In contrast, in indirect sensitization, host-derived (i.e., limbal) APCs infiltrate the graft, and pick up and process alloantigens that they present in the context of host-type MHC class II to self-restricted T cells.\textsuperscript{61} Because the cornea was always said to be devoid of bone-marrow–derived MHC class II cells, the role of the direct pathway has been thought to be either nonexistent or consequential.\textsuperscript{51,44}

Hence, in the context of these different pathways to allosensitization, the central question as to the functionality of the cornea (or graft)–borne cells remained whether they were capable of direct priming of host T cells. To answer this question, we used the highly sensitive ELISPOT method to assay for the frequency of host T-cells primed directly by donor APCs. Lymph node cells were harvested after transplantation, and the T-cells were column-purified before coincubation with donor APC stimulators. Capture monoclonal antibodies were then used to determine the frequency of the direct T-cell response. Our data clearly demonstrate that in high-risk corneal transplantation (grafting onto inflamed recipient beds), but not in low-risk grafting (grafting onto normal and uninflamed host beds), there is significant induction of IL-2- and IFN-γ-secreting, directly primed CD4\textsuperscript{+} T cells well before the onset of clinical rejection (Huq S, et al. \textit{JOVS} 2002;43;ARVO E-Abstract 2275). Are these directly primed T cells relevant in terms of corneal graft rejection? The answer is a resounding yes: Indeed, MHC class II–knockout donor corneas (by definition incapable of priming a host CD4\textsuperscript{+} T cell response) when grafted onto high-risk host beds are rejected at a significantly lower frequency and rapidly than are wild-type donor corneas. Importantly, even when the direct pathway is blocked by using class II–knockout donors, the frequency of rejection is still higher than that normally occurring in low-risk transplantation, suggesting that the indirect pathway continues to play a distinct, though not exclusive, role in host sensitization in high-risk transplantation (Huq, et al. \textit{JOVS} 2003;44;ARVO E-Abstract 3211).

Taken together, two fundamental conclusions can be drawn from these results. First, these data are the first to illustrate definitively the direct contribution of cornea-derived cells in generating the immune response to corneal (in this case allo-)antigens. Second, these data illustrate, to our knowledge for the first time, how the microenvironmental specificities of the transplantation site (e.g., the degree of inflammation or vascularity) can have a profound effect on the differential contribution of the distinct pathways of sensitization generated in the host in response to grafted antigens. An important corollary of this finding is that the strategies used to modulate immunity to allografts (i.e., directed at host-versus-donor factors) may have to be fundamentally different, depending on the type of graft (high-risk versus low-risk) performed.

\textbf{Molecular Regulation of Corneal APC Trafficking to Lymph Nodes}

The data summarized herein suggest that corneal bone-marrow–derived cells are capable of trafficking relatively efficiently to lymphoid organs and functioning as APCs for priming T cells. Indeed, the rapidity of this trafficking and expression of MHC antigens by these cells clearly debunks the myth that antigenic sequestration is the principal barrier to immune reactivity to corneal antigens. But how do these cells so readily gain access to lymphoid reservoirs? And how is this trafficking possible, particularly since the cornea is not only avascular, but more importantly (from the standpoint of APC trafficking), also without lymphatics? There are two explanations: one microanatomical and the other functional. First, although the cornea is lymphatic-free, lymphatic vessels can readily grow into it on inflammatory stimulation\textsuperscript{62,63}; moreover, the conjunctiva is lymphatic rich and so corneal APCs may, at least theoretically, readily gain access to these lymphatics on (centrifugal) migration beyond the limbus. Second, we have recently determined that the same molecular mechanisms that regulate corneal lymphangiogenesis also mediate APC trafficking into afferent lymphatics. How is this possible? The answer to this lies with signaling mediated by vascular endothelial growth factor receptor (VEGFR)-3, a receptor that is distinct from VEGFR-1 (flt-1) and VEGFR-2 (flt-2) that regulate blood angiogenesis.\textsuperscript{64,65} The ligands to VEGFR-3 are VEGF-c and VEGF-d, both of which can serve as growth factors for lymphatic endothelium\textsuperscript{66,67} and hence can result in lymphangiogenesis. We have recently discovered that VEGF-3 overexpression by endothelial cells in response to inflammation or accompanying is also accompanied by surface expression of VEGF-3 by mature (but not immature) corneal DCs.\textsuperscript{69} Indeed, we have shown that in corneal inflammation, the DCs and monocytes that congregate around the budding lymphatics are nearly all VEGFR-3\textsuperscript{+}, suggesting that they may respond to the same signals (e.g., VEGF-c) that induce lymphatic growth into the cornea.\textsuperscript{70} The selective expression of VEGF-3 by corneal CD11c\textsuperscript{+} DCs, but not by stromal keratocytes, has recently been confirmed by flow cytometry (Chen L, et al. \textit{JOVS.} 2003;44:ARVO E-Abstract 701).\textsuperscript{69} To confirm that the expression of VEGF-3 by corneal DCs is indeed functional, we have recently performed transwell chemotactic assays with corneal DCs (cultured from corneal explants) and have shown a dose-dependent chemotactic response to VEGF-c. This chemotaxis could be blocked by a VEGF-3/Ig chimeric molecule that suppresses VEGF-3–mediated signaling (Chen, et al. \textit{JOVS} 2003;44:ARVO E-Abstract 701). To demonstrate conclusively the in vivo relevance of

\textbf{Regression of Corneal APC Trafficking to Lymph Nodes}
these findings, we have quantified the trafficking of graft-derived APCs after transplantation to ipsilateral lymph nodes, either after subconjunctival injection of VEGFR-3/Flk1 or a control Flk1. We have shown that by blocking local VEGFR-3 signaling, we can profoundly suppress the migration of corneal APCs to regional draining lymph nodes. Does blockade of this pathway impede graft rejection? Herein we describe our recent findings that the functional relevance of a single molecular pathway (e.g., CD154 or VEGFR-3) can have profound effects on immunity through regulating highly disparate mechanisms (suppression of costimulation versus APC trafficking).

**Figure 1.** Graphic representation of the mechanisms involved in induction of immunity by corneal APCs. Corneal expression of proinflammatory cytokines (e.g., IL-1 and TNF-α) and chemokines in response to antigenic challenge (or other ‘danger signals’) leads to recruitment of innate immune cells, followed rapidly by influx of CD11c⁺ DC/LC elements from the limbus into the cornea. Expression of ICAM-1 by the VECs plays a critical role in initiating this process. These cells, along with the heterogeneous bone marrow elements that are normally resident in the cornea, express VEGFR-3 in response to inflammation—a process that coincides temporally with these cells’ acquisition of maturation markers, including MHC class II and B7 (CD80, CD86) costimulatory molecules. In response to VEGF-c, the VEGFR-3⁺ cells are recruited to afferent lymphatics that serve as conduit for these APCs to gain access to high concentrations of naive T cells present in the parafollicular areas of the lymph nodes. Ligation of CD40 on APCs by CD154 (CD40L) expressed by CD4 T cells leads to release of IL-12 and induction of T helper-1 response to corneal antigens presented by the APCs.

**T-CELL PRIMING: THE COMMON DENOMINATOR OF ADAPTIVE IMMUNITY**

So far, we have focused almost exclusively on the trafficking of APCs from the intravascular compartment to the corneal tissue matrix and from the cornea to lymphoid organs by gaining access to afferent lymphatics through VEGFR-3 signaling. However, it is critical to emphasize that the functional relevance of this traffic is to bring the antigen-bearing APCs in intimate contact with a large number of naïve T cells in lymphoid reservoirs (such as the lymph node) for priming of antigen-specific immunity. By dissecting the molecular mechanisms involved in this trafficking, we have identified multiple steps that can be targeted, with resultant suppression of immune responsiveness.

The fact that the common denominator in generating an adaptive immune response is the priming of T cells, rather than any one of the steps related to APC trafficking as we have outlined, has been confirmed by our studies focusing on blocking the interaction of CD40 with CD40 ligand (CD40L, also known as CD154). CD40 is a critical costimulatory molecule expressed by many APCs (including corneal DCs and LCs), whose ligation by CD154 leads to overexpression of CD80 (B7.1), CD86 (B7.2), and IL-12—critical factors in priming a T helper-1 response. We have provided conclusive evidence that administration of anti-CD154 can block both the direct and indirect pathways of allosensitization, thereby promoting immunologic ‘ignorance’ (based on failure to induce T-cell priming) but without promoting active tolerance or significant T helper-2 skewing. Indeed, in corneal transplant hosts treated with anti-CD154, DTH fails to develop in response to corneal antigens, and they demonstrate near-universal acceptance of corneal allografts, even in the high-risk setting, as long as the systemic treatment is sustained.

It is important to emphasize the mechanisms we have focused on, namely those that regulate APC infiltration into the cornea and their mobilization to lymphatics, and finally priming of naïve T cells, all comprise the sensitization (or afferent) arm of the alloimmune response (Fig. 1) in contrast to the effector (or efferent) mechanisms that mediate the T cell targeting of the graft. Indeed, once primed, alloreactive effector T cells must undergo clonal expansion, peripheralize, and target the graft before any demonstrable clinical rejection. Our preliminary data suggest that these effector processes are mediated by wholly different chemokine systems (mediated by CCR1 and CXCR3) than those that mediate the ingress of immature APCs into the cornea, as we described earlier in the lecture. Finally, we want to emphasize that, as elaborate and redundant as the mechanisms that regulate immunity are, the data described herein clearly demonstrate that blockade of even one molecular pathway (e.g., CD154 or VEGFR-3) can have profound effects on immunity through regulating highly disparate mechanisms (suppression of costimulation versus APC trafficking).

**IMPLICATIONS AND CONCLUDING REMARKS**

In conclusion, we have demonstrated that the normal cornea in fact possesses a heterogeneous population of resident bone-marrow–derived cells, including DCs. These cells have the unique feature of being universally immature or of a precursor phenotype and hence have the ‘disguising’ feature of being ubiquitously MHC class II–negative, and many of these cells, including the DCs, have the functional pliability of migrating out of the cornea, overexpressing requisite costimulatory molecules, presenting antigen, and stimulating T cells under inflammatory conditions. Moreover, we have shown how the processes that mediate the ingress of these APC populations into the cornea during inflammation are distinct from those that mediate the egress of these cells into lymphatics, demonstrating how the modulation of each of these steps can affect induction of immunity to corneal antigens.

Many critical issues remain unresolved. For example, it is thought that resident APCs in the periphery are recruited from the intravascular compartment. Given that the bone marrow elements we have identified in the cornea are universally MHC
class II-negative, whereas only a small population of similar cells in the blood are in such a premature state, there are two relevant questions: Where do the corneal cells come from, and what microenvironmental factors suppress the maturity state of these leukocytes as they gain entry into the normal cornea? Finally, whereas we have focused on the role of these resident bone marrow elements in inducing immune responsiveness, it is critical to determine what role, if any, these cells may have in the induction of tolerance.

Although we expect that ongoing investigations will eventually provide insights into the answers to these questions, it is also important to emphasize the general implications of these findings in terms of our understanding of corneal physiology and immunopathology. Whether it has been generation of immunity to transplants or innate immune responses to infection or injury, the cornea has historically been seen as a simple collagenous tissue at the mercy of the host immune system. The novel findings described herein may lead to a paradigm shift in our understanding of corneal immunity as we move away from the concept of the cornea as a passive bystander, to a model in which it incorporates its role as an active participant in orchestrating the immune system in response to foreign or autoantigens.

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