Effect of Donor Langerhans Cells on Corneal Graft Rejection

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Unlike other cutaneous surfaces, the central portion of the corneal epithelium is typically devoid of Langerhans cells. The absence of Ia+ Langerhans cells in the central cornea is of more than casual interest and may explain the immunologic privilege that is characteristic of corneal allografts. The present communication summarizes previous studies that examined the role of corneal Langerhans cells in eliciting alloimmune responses and corneal graft rejection in rodents. Under normal circumstances, corneal allografts are poorly immunogenic when residing in the avascular ocular graft bed even though the graft displays large quantities of alloantigens. The afferent blockade of the immune response can be circumvented by donor-derived Langerhans cells that serve as potent immunogens for all categories of corneal allografts except grafts involving allodisparity only at class I major histocompatibility complex loci. Thus, the presence of donor-derived Langerhans cells exerts profound effects on the fate of corneal allografts. *J Invest Dermatol 99:104S–106S, 1992*

Corneal transplantation is arguably the oldest and most successful form of solid tissue transplantation. The first documented successful human corneal transplant was performed at the turn of this century [1]. During the ensuing 75 years, literally thousands of corneal transplants have been performed on human subjects. In the United States alone, over 30,000 corneal transplants are performed each year with a rejection rate less than 10% [1]. This extraordinary success rate is particularly impressive considering that patients are not routinely tissue typed and do not normally receive systemic immunosuppressive drugs.

The apparent ease with which corneal transplants escape immunologic rejection has been attributed to the conspicuous absence of blood and lymphatic vessels in the corneal graft bed [2]. Indeed there is a large body of evidence to support the notion that the avascular corneal graft bed produces an afferent blockade of the systemic immune apparatus due to the sequestration of alloantigens [2]. We have proposed that, in addition to the avascular nature of the corneal graft bed, the unique absence of donor-derived Langerhans cells in the cornea contributes to the immunologic privilege of corneal allografts [1,2].

The central portion of the cornea of humans, as well as a wide range of mammalian species, is typically devoid of Langerhans cells [1,2]. Indeed, the absence of Ia+ Langerhans cells in the central cornea is of more than casual interest, because these cells represent an important immunogenic component of the allograft. It has been suggested that Ia+ "passenger cells" are important immunogens and represent the major barrier to successful organ transplantation [3]. The consistent absence of Langerhans cells in that portion of the cornea normally used for corneal transplantation offers an unusual opportunity to examine the role of "passenger cells" in general and Langerhans cells in specific, in the elicitation of alloimmune responses and allograft rejection. This review summarizes our efforts to evaluate the role of donor-derived Langerhans cells in eliciting corneal allograft rejection. In particular, we wished to determine the effect of donor-derived Langerhans cells in the context of specific categories of histocompatibility antigens.

DYNAMIC DISTRIBUTION OF CORNEAL LANGERHANS CELLS

Under normal circumstances, corneal Langerhans cells (LC) are organized in a well-defined, circumferential pattern in the transitional area between the peripheral cornea and the conjunctiva. Corneal LC are capable of migrating from the periphery to the central regions of the cornea following various stimuli including electrocautery [4], bacterial and viral infections [5,6], and phagocytic stimuli [7]. We have shown that instillation of 1.0-μ sterile latex beads into shallow epithelial incisions induces rapid, centripetal migration of peripheral LC into the central portions of the cornea [7]. Such "latex bead–treated," LC-containing corneas can be utilized as corneal grafts and compared to untreated corneal grafts as a facile method for evaluating the role of donor-derived LC in initiating allograft rejection.

CORNEAL GRAFTS MISMATCHED AT THE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) AND MULTIPLE MINOR H LOCI (=FULLY ALLOGENEIC)

All of the results reported here were from studies utilizing a well-characterized orthotopic corneal allograft model in the rat [8]. The effect of donor-derived LC was assessed in a fully allogeneic donor-host combination [8]. The immunologic privilege of corneal allografts was apparent by the high success rate of LC-free corneal allografts that underwent rejection in only 55% of the naive hosts [8]. By contrast, 96% (22 of 23) of the LC-containing grafts were rejected with a mean survival time (MST) of 11.8 ± 5.2 d [8]. The presence of donor-derived LC greatly enhanced the immunogenicity of the fully allogeneic corneal allografts that was demonstrated by significant elevation of the cytotoxic T-lymphocyte responses

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Abbreviations:
LC: Langerhans cells
MHC: major histocompatibility complex
MST: mean survival time

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Table I. Rejection of Class I MHC Disparate Cornea Allografts[a]

First Graft (Day 0)	Second Graft (Day 30)	Percent Corneal Graft Rejection
Cornea (LC−)	—	18%
Cornea (LC+)	—	20%
Skin	Cornea	100%
Cornea (LC−)	Skin	100%

[a] Details of the experiment are published elsewhere [9].

[8]. Thus, the presence of donor LC virtually assured the rejection of fully allogeneic corneal allografts.

REJECTION OF CORNEAL ALLOGRAFTS MISMATCHED ONLY AT CLASS I MHC LOCI

Experiments similar to those described above were performed using congenic rat strains differing only at the class I MHC locus [9]. Although hosts pre-immunized with skin grafts always rejected subsequent class I MHC disparate corneal grafts from the same donor (100% rejection; MST = 13.3 ± 2.2 d), corneal grafts were rejected in only 18% of the naive hosts (Table I). Surprisingly, the presence of donor LC did not increase the rejection of class I MHC disparate grafts. Even though the class I MHC disparate grafts were poorly immunogenic, they were highly antigenic. Hosts subsequently immunized with donor skin grafts rejected both the class I disparate skin grafts and the previously clear corneal allografts. Thus, the corneal graft bed provides afferent but not efferent blockade of the immune apparatus in terms of class I MHC alloantigens. Unlike the case of fully allogeneic grafts, the presence of donor-specific LC does not circumvent the immunologic privilege extended to class I disparate corneal grafts.

REJECTION OF CORNEAL ALLOGRAFTS MISMATCHED ONLY AT CLASS II MHC LOCI

Studies involving corneal allografts exchanged between rat strains differing only at class II MHC loci provided important insights into the regulation of class II MHC antigens in the cornea [10]. Because none of the cells of the cornea normally express class II antigens, it was not surprising that none of the class II disparate grafts underwent rejection (Table II). However, hosts pre-immunized with skin grafts rejected subsequent LC-free, class II disparate corneal allografts. This apparent paradox, in which grafts that were presumably class II MHC negative were rejected, was explained by the regulation of class II MHC antigens on the corneal cells. LC-free corneal grafts were removed and examined by immunofluorescence for the expression of donor class II MHC antigens at 24-h intervals following transplantation onto naive hosts. Within 24 h of grafting, over 25% of the corneal epithelial cells expressed class II MHC antigens and, by day seven, 100% of the cells displayed strong expression of class II MHC antigens [10]. By day 10, all of the corneal epithelial cells had returned to their original class II negative phenotype. Thus, the surgical procedure itself induced swift, albeit transient, expression of class II MHC antigens on the corneal allografts. In the case of the naive host receiving its first corneal allograft, the expression of class II MHC antigens dissipates before immunologic effector cells have been generated. By contrast, in the pre-immune host, the class II antigens induced by surgery provide targets for immunologic attack by the pre-existing immune effector cells. Although the presence of donor-derived LC did not lead to the rejection of primary corneal allografts, it did elicit potent systemic alloimmunity that culminated in swift rejection of subsequent LC-free corneal allografts transplanted to the contralateral eye.

Table II. Rejection of Class II MHC Disparate Corneal Allografts[a]

First Graft	Second Graft	Percent Rejection (Second Graft)
Cornea	none	0%
LC + Cornea	none	0%
Skin	Cornea (LC−)	100%
LC + Cornea	Cornea (LC−)	80%
LC − Cornea	Cornea (LC−)	0%

[a] Details of experiment are described elsewhere [10].

Table III. Rejection of MHC Matched, Multiple Minor H Mismatched Corneal Grafts[a]

Graft	Percent Rejection
LC − Cornea	26%
LC + Cornea	59%
LC − Cornea (Preimmune host)[b]	100%
LC − Cornea (Late latex bead)[c]	10%

[a] Details of original experiment described elsewhere [10].
[b] Hosts pre-immunized with skin grafts from same donor that provided subsequent corneal allograft.
[c] Long-term surviving multiple minor H disparate corneal grafts were treated with latex beads (>60 d post-transplantation) to induce centripetal migration of Host LC into corneal allograft.

REJECTION OF CORNEAL ALLOGRAFTS MISMATCHED ONLY AT MULTIPLE MINOR H LOCI

The effect of donor LC on the rejection of MHC-identical, multiple minor H disparate corneal grafts was assessed [11]. As in all previous combinations, hosts pre-immunized with skin grafts always rejected subsequent corneal grafts. In naive hosts, however, the immunologic privilege of minor H disparate grafts was apparent — rejection occurred in only 26% of the non-immune hosts (Table III). The presence of donor LC increased the alloimmunogenicity of these grafts significantly — rejection occurred in 59% of the latex bead–treated corneal grafts. Further experiments evaluated the effect of the recipient's LC on the fate of MHC matched, minor H disparate corneal grafts. Long-term surviving corneal grafts (>60 d post grafting) were treated with latex beads to induce the migration of the recipient's own LC. Infiltration of corneal grafts with recipient LC did not affect the survival of multiple minor H disparate corneal grafts as only one of ten such grafts underwent rejection. Thus, the presence of *donor* LC greatly increases the immunogenicity and subsequent rejection of corneal grafts matched at the MHC but mismatched at multiple minor H loci. Infiltration of the surviving grafts with recipient LC, however, does not jeopardize graft survival or provoke alloimmunity.

CONCLUSION

The results summarized here indicate that the presence of donor-derived LC can have a profound influence on the immunogenicity and fate of corneal allografts. Under normal circumstances, corneal allografts are poorly immunogenic when residing in the avascular ocular graft bed even though the graft displays abundant quantities of alloantigens. This afferent blockade of the immune response can be circumvented by donor-derived LC that serve as potent immunogens for all categories of corneal allografts except grafts involving allodisparity only at class I MHC loci. Thus, the remarkable immunologic privilege of corneal allografts can be attributed to the avascular nature of the corneal graft bed, the absence of lymphatic drainage of the graft site, and the absence of donor-derived LC. One wonders if the occasional rejection of the human corneal allografts is the

result of the transplantation of an aberrant corneal graft that contains donor-derived LC.

REFERENCES

1. Niederkorn JY: Immune privilege and immune regulation in the eye. Adv Immunol 48:199–226, 1990
2. Niederkorn JY, Peeler JS: Regional differences in immune regulation: the immunogenic privilege of corneal allografts. Immunol Res 7:247–255, 1988
3. Austyn JM, Steinman RM: The passenger leukocyte—a fresh look. Transplant Rev 2:139–176, 1988
4. Williamson JSP, DiMarco S, Streilein JW: Immunobiology of Langerhans cells on the ocular surface. I. Langerhans cells within the central corneal interfere with induction of anterior chamber associated immune deviation. Invest Ophthalmol Vis Sci 28:1527–1532, 1987
5. Hazlett LD, Moon M, Dawisha A, Berk RS: Age alters ADP positive dendritic (Langerhans) cell response to *Pseudomonas aeruginosa* challenge. Curr Eye Res 5:343–355, 1986
6. Lewkowicz-Moss SJ, Shimeld C, Lipworth K, Hill TJ, Blyth WA, Easty DL: Quantitative studies on Langerhans cells in mouse corneal epithelium following infection with herpes simplex virus. Exp Eye Res 45:127–140, 1987
7. Niederkorn JY, Peeler JS, Mellon J: Phagocytosis of particulate antigens by corneal epithelial cells stimulates interleukin-1 secretion and migration of Langerhans cells into the central cornea. Region Immunol 2:83–90, 1989
8. Callanan D, Peeler JS, Niederkorn JY: Characteristics of rejection of orthotopic corneal allografts in the rat. Transplantation 45:437–443, 1988
9. Ross J, He Y-G, Niederkorn JY: Class I disparate corneal grafts enjoy afferent but not efferent blockade of the immune response. Curr Eye Res 10:889–892, 1991
10. Ross J, Callanan D, Kunz H, Niederkorn J: Evidence that the fate of class II–disparate corneal grafts is determined by the timing of class II expression. Transplantation 51:532–536, 1991
11. Ross J, He Y-G, Pidherney M, Mellon J, Niederkorn JY: The differential effects of donor versus host Langerhans cells in the rejection of MHC-matched corneal allografts. Transplantation 52:857–861, 1991