Published in final edited form as:
*Curr Opin Allergy Clin Immunol*. 2010 October ; 10(5): 493–497. doi:10.1097/ACI.0b013e32833dfa11.

# High risk corneal allografts and why they lose their immune privilege

**Jerry Y. Niederkorn**
Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, Texas 75390 U.S.A

## Abstract

**Purpose of review—**Corneal allografts are routinely performed without HLA typing or systemic immunosuppressive drugs. However, certain conditions create high risks for immune rejection. This review discusses recent insights into the mechanisms that rob the corneal allograft of its immune privilege.

**Recent findings—**Studies in mice have revealed that stimuli that induce new blood vessel growth in the cornea also elicit proliferation of lymph vessels. Lymph vessels facilitate migration of antigen presenting cells to regional lymph nodes where they induce alloimmune responses. The presence of blood vessels in the corneal graft bed creates a unique chemokine milieu that stimulates recruitment of sensitized lymphocytes into the corneal allograft. Other data indicate that corneal allograft survival is closely associated with Foxp3 expression in $CD4^+CD25^+Foxp3^+$ T regulatory cells (Tregs), while reduced expression of Foxp3 in T regs creates a high risk for graft rejection. Recent evidence indicates that allergic diseases have a profound impact on the immune response and produce a dramatic increase in corneal allograft rejection.

**Summary—**Understanding the underlying mechanisms that create “high risk” hosts may provide important therapeutic targets for restoring immune privilege of corneal allografts and enhancing their survival.

### Keywords

Allergy; angiogenesis; corneal transplantation; immune privilege

## Introduction

Cornea grafting has been performed on humans for over 100 years and remains the most common and arguably, the most successful form of organ transplantation [1–4]. First-time corneal transplants are routinely performed without HLA matching or systemic immunosuppressive drugs. Patients who require transplants because of corneal developmental anomalies, such as keratoconus, do not have inflamed or vascularized corneal graft beds and have an exceptionally high acceptance rate that often exceeds 90%. In these patients topical application of corticosteroids is usually all that is needed to keep the immune system at bay [5].

Corresponding Author: Jerry Y. Niederkorn (jerry.niederkorn@utsouthwestern.edu).
The author has no conflicts of interest to report.

## Immune privilege of corneal allografts

lmmune privilege of the eye was recognized over 50 years ago by Billingham and Medawar who noted the prolonged survival of skin allografts placed into the anterior chamber of the eye and the acceptance of orthotopic corneal allografts placed onto the eyes of rabbits [6,7]. Medawar understood the significance of these observations and coined the term “immune privilege” to reflect the cornea’s apparent exemption from the laws of transplantation [7].

Tangible evidence of immune privilege is shown in rodents in which long-term survival of fully allogeneic corneal allografts often exceeds 50% even in the absence of topical corticosteroids [2–4]. By contrast, other categories of allografts, such as skin transplants, experience a 100% incidence of immune rejection.

Although corneal transplantation has been performed on experimental animals since 1837 [8], it was not until the development of rodent models of penetrating keratoplasty that the immunological basis of corneal allograft rejection was fully appreciated [9,10]. The past 20 years of animal research have provided keen insights into the processes that provide corneal allografts with immune privilege [1–3,11–13]. Immune privilege of corneal allografts is the product of three fundamental adaptations that: a) block the induction of destructive alloimmune responses; b) deviate alloimmune responses toward a tolerogenic pathway; and c) block expression of immune effector elements at the graft/host interface (Table 1).

## Role of immune deviation and T regulatory cells in corneal allograft survival

Antigens placed into the anterior chamber (AC) elicit a form of systemic immune tolerance called anterior chamber-associated immune deviation (ACAID), which is characterized by the antigen-specific down-regulation of delayed-type hypersensitivity (DTH) responses and a shifting of the antibody response from complement-fixing to non-complement fixing isotypes [13–16]. Orthotopic corneal allografts are in direct contact with the AC and it has been suggested that corneal antigens are sloughed into the AC during corneal transplantation and induce ACAID [13]. In support of this is the observation that long-term corneal allograft survival in mice closely correlates with the presence of antigen-specific suppression of DTH responses to donor alloantigens that closely resembles ACAID [13,16,17]. Likewise, manipulations that block the induction of ACAID result in a significant increase in corneal allograft rejection [13,18–21].

Recent findings have shed light on the role of T regulatory cells in maintaining immune privilege of corneal allografts. Examination of the draining lymph nodes in mice that had either rejected or accepted orthotopic corneal allografts revealed that both categories of mice expressed equal numbers of $CD4^+CD25^+Foxp3^+$ T regulatory cells (T regs) [22]. However, T regs isolated from mice with accepted corneal allografts (= acceptors) displayed ~50% higher levels of Foxp3 than T regs in rejector mice. Moreover, Tregs from acceptors were significantly more effective in suppressing T cell proliferation and produced up to 3-fold more suppressive cytokines compared to T regs from rejectors. Adoptively transferring T regs from acceptors into naïve recipients resulted in 67% long-term corneal allograft survival compared to 33% graft survival in mice that received T regs from graft rejectors. Thus, long-term survival of corneal allografts rests on the development of $CD4^+CD25^+Foxp3^+$ and the level of Foxp3 expression in those T regs.

## Effect of lymph and blood vessels on the immune privilege of corneal allografts

One of the most recognizable properties of the cornea is the conspicuous absence of blood vessels. Less apparent, but equally important, is the exclusion of lymph vessels in the corneal graft bed [23–26]. It was widely believed that the presence of blood vessels increased the risk for immune rejection by providing conduits for egression of alloantigens to the peripheral immune apparatus and by also facilitating the migration of circulating effector immune elements into the corneal allograft. However, recent findings indicate that many of the stimuli that induce new blood vessels in the graft bed coincidentally stimulate migration and penetration of lymph vessels along with the blood vessels.

Inserting sutures into the cornea is a powerful stimulus for inducing new blood and lymph vessels. However, administration of an antagonist of α5β1 integrin selectively inhibits the induction of lymphangiogenesis while preserving hemangiogenesis in response to intracorneal sutures [26]. Importantly, blocking lymphangiogenesis reduces the incidence of corneal allograft rejection to levels found in mice with avascular corneal graft beds, even though the corneal allografts in the former experiment were placed in graft beds containing blood vessels.

VEGF-C and VEGF-D bind to VEGF receptor 3 (VEGFR3) and induce blood and lymph vessel formation in the cornea [24,27]. Soluble VEGF receptors suppress both hemangiogenesis and lymphangiogenesis [25]. It has recently been shown that corneal epithelial and stromal cells secrete a soluble form of VEGFR2, which blocks VEGF-C and prevents lymphangiogenesis in the cornea without affecting hemangiogenesis [23]. Local production of VEGFR2 by the corneal epithelium and stroma preserves the avascularity of the cornea. The importance of the soluble form of VEGFR2 in preventing lymph vessel invasion of the cornea was demonstrated in studies in which tissue-specific expression of soluble VEGFR2 was ablated in the cornea using Cre-*loxP* technology. Mice unable to express soluble VEGFR2 at birth developed corneas that were densely supplied with lymphatic vessels but were devoid of blood vessels [23]. Moreover, administration of soluble VEGFR2 inhibited lymph vessel formation in normal mice and enhanced corneal allograft survival even if the corneal graft beds had a dense network of blood vessels that were induced by the sutures [23].

Lymph vessels rob the corneal allograft of its immune privilege by providing conduits for antigen presenting cells to traffic from the graft bed to the regional lymph node where they induce the activation and clonal expansion of alloantigen-specific T cells. Activated T cells subsequently migrate to the graft bed and initiate graft rejection. Recruitment of allospecific effector T cells to the allograft is a crucial step in the rejection of vascularized organ allografts and is influenced by the chemokines that emanate from the allograft [28–34]. Amescua and coworkers hypothesized that a similar condition might occur in “high-risk” corneal allografts in which the insertion of sutures induced a luxuriant growth of blood vessels [35]. They found that “high-risk” vascularized corneal allografts produced the T cell chemokine, CXCL1/KC, which in turn stimulated the production of other T cell chemokines, CXCL9/Mig and CXCL10/IP10, which are intimately involved in recruitment of allospecific T cells into vascularized grafts [28–34]. Moreover, increased levels of CXCL-1/KC that were found in vascularized “high risk” corneal allografts were not present in non-vascularized, normal-risk corneal allografts. “High-risk” hosts treated with neutralizing anti-CXCL-1/KC antibody behaved like normal risk hosts with avascular graft beds. Likewise, administration of CXCL-1/KC into the corneal allograft converted low-risk hosts to a high-risk phenotype resulting in 100% corneal allograft rejection, thereby confirming the important effect of the chemokine milieu in abrogating the immune privilege

of corneal allografts. Thus, the presence of blood and lymph vessels in “high-risk” hosts also ablates immune privilege of corneal allografts by promoting migration, recruitment, and infiltration of immune effector elements into the corneal allograft and thus, enhances the efferent arm of the immune response.

## Allergic diseases as newly recognized risk factors for corneal allograft rejection

It was previously believed that the rejection of corneal transplants, was solely mediated by $CD4^+$ Th1 cells and that tilting the immune response toward a Th2 pathway would promote graft survival. However, recent evidence not only refutes this proposition, but suggests that the opposite may occur. Deviating the alloimmune response to a Th2 immune response by elimination of the Th1 cytokine, interferon-γ (IFN-γ), or by inducing allergic diseases, denies the corneal allograft its immune privilege and promotes corneal allograft rejection [36–40]. IFN-γ knockout (KO) mice or wild-type mice treated with anti-IFN-γ antibody reject 90–100% of their corneal allografts compared to a 50% incidence of rejection in normal mice [38].

Clinicians have noted that patients with severe ocular allergies have an elevated risk for corneal graft rejection [41–43]. It was thought that the increased rejection of corneal allograft that was associated with conjunctivitis was due to the effects of a “hot eye” and inflammation produced by local allergic responses. However, studies in mice indicate that allergic diseases do in fact exacerbate corneal allograft rejection, but the mechanism is through perturbation in the systemic alloimmune response and not to local effect as previously suspected [36,37,39]. Mice with allergic conjunctivitis that was intentionally limited to one eye, experienced a >90% incidence of corneal allograft rejection when a corneal allograft was placed into the contralateral eye that was not expressing allergic conjunctivitis [36]. Moreover, mice with airway hyperreactivity (AHR), which is a model of allergic asthma, reject 90–100% of the corneal allografts compared to a 50% incidence of rejection in non-allergic mice [40]. The increased corneal allograft rejection in mice with allergic diseases in different organs (i.e., lungs or contralateral eye) is further evidence that allergic diseases exert a systemic, rather than a local effect in corneal allograft rejection.

Recent investigations have shown that the increased rejection of corneal allografts in mice with allergic conjunctivitis and AHR is limited to allergic diseases of mucosal tissues, as it does not occur in mice with cutaneous immediate hypersensitivity [39]. The notion that classical Th2 immune responses, such as allergic disease, are monolithic and occur in the absence of the Th1 cytokine, IFN-γ, is losing favor and there is mounting evidence that IFN-γ is necessary for full expression of Th2 diseases [44–46]. The exacerbation of corneal allograft rejection that occurs in allergic conjunctivitis appears to also require Th1 cells. Adoptively transferring unfractionated $CD4^+$ T cells from allergic mice to T cell-deficient nude mice induced 100% corneal allograft rejection compared to 0% rejection in nude mice that did not receive $CD4^+$ T cells [39]. However, adoptive transfer of $CD4^+$ Th1 cells alone or $CD4^+$ Th2 cells alone resulted in 70% and 20% rejection respectively, while combining Th1 and Th2 cells produced 100% graft rejection. Interestingly, administration of exogenous IFN-γ could substitute for Th1 cells and produced 100% corneal allograft rejection when combined with $CD4^+$ Th2 cells. Thus, allergic diseases of mucosal surfaces exacerbate corneal allograft rejection by activating both Th1 and Th2 alloimmune responses and represent a new risk factor for corneal allograft rejection (Table 2). The mechanisms responsible for the increased incidence and tempo of rejection remain to be elucidated, but once understood, could provide important clues for restoring the immune privilege of corneal allografts in atopic patients.

## Conclusions

Mouse studies have provided a wealth of information regarding the immunobiology and immune privilege of corneal allografts. The association between vascularized graft beds and increased corneal allograft rejection has been recognized for over a half century. However, it was only recently that the role of lymph vessels was demonstrated. Lymph vessels enhance the induction of immune responses, while the presence of blood vessels facilitates recruitment and migration of sensitized immune effector cells into the graft. Recognition of this dichotomy opens the door for targeted therapy for enhancing corneal allograft survival.

The role of $CD4^+CD25^+Foxp3^+$ T regs in preventing corneal allograft rejection has been recently demonstrated. However, the mere expression of Foxp3 alone is not sufficient for promoting corneal allograft survival; instead it is the intensity of Foxp3 expression and the functional properties of T regs that correlate with corneal allograft survival. These insights may provide clues for developing new strategies for restoring immune privilege in the high-risk host.

The last 2–3 years have witnessed the characterization of allergic diseases as a new risk factor for corneal allograft rejection. These studies have revealed that Th2-based immune responses in mucosal tissues dramatically increase the risk for corneal graft rejection. It will be important to determine the underlying mechanisms that are responsible for the increased tempo and incidence of corneal allograft rejection that occurs in hosts with mucosal allergic diseases.

## Acknowledgments

This work was supported by National Institutes of Health grants EY007641 and an unrestricted grant from Research to Prevent Blindness.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest.

1. George AJ, Larkin DF. Corneal transplantation: The forgotten graft. Am J Transplant. 2004; 4:678–685. [PubMed: 15084160]
2. Niederkorn JY. The immune privilege of corneal allografts. Transplantation. 1999; 67:1503–1508. [PubMed: 10401754]
3. Niederkorn JY. The immune privilege of corneal grafts. J Leukoc Biol. 2003; 74:167–171. [PubMed: 12885932]
4. Niederkorn JY. Immune mechanisms of corneal allograft rejection. Curr Eye Res. 2007; 32:1005–1016. [PubMed: 18085464]
5. Group CCTSR. The collaborative corneal transplantation studies (CCTS). Effectiveness of histocompatibility matching in high-risk corneal transplantation. Arch Ophthalmol. 1992; 110:1392–1403. [PubMed: 1417537]
6. Billingham RE, Boswell T. Studies on the problem of corneal homografts. Proc R Soc Lond B Biol Sci. 1953; 141:392–406. [PubMed: 13074176]
7. Medawar PB. Immunity to homologous grafted skin. III. The fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. Br J Exp Pathol. 1948; 29:58–69. [PubMed: 18865105]

8. Bigger SL. An inquiry into the possibility of transplanting the cornea with the view of relieving blindness (hitherto deemed incurable) caused by several diseases of that structure. Dublin J Med Sci. 1837; 11:408–447.

9. She SC, Steahly LP, Moticka EJ. A method for performing full-thickness, orthotopic, penetrating keratoplasty in the mouse. Ophthalmic Surg. 1990; 21:781–785. [PubMed: 2270163]

10. Williams KA, Coster DJ. Penetrating corneal transplantation in the inbred rat: A new model. Invest Ophthalmol Vis Sci. 1985; 26:23–30. [PubMed: 3881365]

11. Niederkorn JY. The immunology of corneal transplantation. Dev Ophthalmol. 1999; 30:129–140. [PubMed: 10627921]

12. Niederkorn JY. Mechanisms of corneal graft rejection: The Sixth Annual Thygeson Lecture, presented at the Ocular Microbiology and Immunology Group meeting, October 21, 2000. Cornea. 2001; 20:675–679. [PubMed: 11588415]

13. Niederkorn JY. Anterior chamber-associated immune deviation and its impact on corneal allograft survival. Current Opinion in Organ Transplantation. 2006; 11:360–365.

14. Niederkorn JY. See no evil, hear no evil, do no evil: The lessons of immune privilege. Nat Immunol. 2006; 7:354–359. [PubMed: 16550198]

15. Niederkorn JY, Stein-Streilein J. History and physiology of immune privilege. Ocul Immunol Inflamm. 18:19–23. [PubMed: 20128645]

16. Streilein JW. Ocular immune privilege: Therapeutic opportunities from an experiment of nature. Nat Rev Immunol. 2003; 3:879–889. [PubMed: 14668804]

17. Sonoda Y, Streilein JW. Impaired cell-mediated immunity in mice bearing healthy orthotopic corneal allografts. J Immunol. 1993; 150:1727–1734. [PubMed: 8436812]

18. Plskova J, Duncan L, Holan V, et al. The immune response to corneal allograft requires a site-specific draining lymph node. Transplantation. 2002; 73:210–215. [PubMed: 11821732]

19. Skelsey ME, Mellon J, Niederkorn JY. Gamma delta T cells are needed for ocular immune privilege and corneal graft survival. J Immunol. 2001; 166:4327–4333. [PubMed: 11254685]

20. Sonoda KH, Taniguchi M, Stein-Streilein J. Long-term survival of corneal allografts is dependent on intact CD-1d-reactive NKT cells. J Immunol. 2002; 168:2028–2034. [PubMed: 11823540]

21. Yamagami S, Dana MR. The critical role of lymph nodes in corneal alloimmunization and graft rejection. Invest Ophthalmol Vis Sci. 2001; 42:1293–1298. [PubMed: 11328742]

22*. Chauhan SK, Saban DR, Lee HK, et al. Levels of Foxp3 in regulatory T cells reflect their functional status in transplantation. J Immunol. 2009; 182:148–153. This study demonstrates that although CD4+CD25+Foxp3+ putative T regs can be detected in both corneal graft rejector and corneal allograft acceptor mice, the level of Foxp3 expression is approximately 50% higher in hosts with surviving grafts. Also, adoptive transfer of T regs doubles the incidence of corneal allograft acceptance. [PubMed: 19109145]

23**. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor receptor-2 is an essential endogenous inhibitor of lymphatic vessel growth. Nat Med. 2009; 15:1023–1030. This study demonstrates that the absence of lymph vessels in the normal corneal is due, at least in part, to the constitutive production of soluble VEGFR2 by corneal cells and has a profound effect in inhibiting lymph vessel proliferation. Administration of exogenous soluble VEGFR2 inhibits lymph vessel growth and produces a dramatic enhancement of corneal allograft survival. [PubMed: 19668192]

24. Cursiefen C, Chen L, Borges LP, et al. VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascularization via macrophage recruitment. J Clin Invest. 2004; 113:1040–1050. [PubMed: 15057311]

25. Cursiefen C, Chen L, Saint-Geniez M, et al. Nonvascular VEGF receptor 3 expression by corneal epithelium maintains avascularity and vision. Proc Natl Acad Sci U S A. 2006; 103:11405–11410. [PubMed: 16849433]

26**. Dietrich T, Bock F, Yuen D, et al. Cutting edge: Lymphatic vessels, not blood vessels, primarily mediate immune rejections after transplantation. J Immunol. 2010; 184:535–539. Although some chemical cues induce both lymph and blood vessel formation in the cornea, it is possible to selectively inhibit lymph vessel proliferation and penetration into the cornea by an antagonist of α5B1 integrin. The selective blockade of lymphangiogenesis enhanced corneal allograft survival,

thus showing the importance of lymph vessels in the abrogation of the immune privilege of corneal allografts. [PubMed: 20018627]

27. Stacker SA, Achen MG, Jussila L, et al. Lymphangiogenesis and cancer metastasis. Nat Rev Cancer. 2002; 2:573–583. [PubMed: 12154350]
28. El-Sawy T, Miura M, Fairchild R. Early T cell response to allografts occurring prior to alloantigen priming up-regulates innate-mediated inflammation and graft necrosis. Am J Pathol. 2004; 165:147–157. [PubMed: 15215170]
29. Fairchild RL, VanBuskirk AM, Kondo T, et al. Expression of chemokine genes during rejection and long-term acceptance of cardiac allografts. Transplantation. 1997; 63:1807–1812. [PubMed: 9210509]
30. Hancock WW, Wang L, Ye Q, et al. Chemokines and their receptors as markers of allograft rejection and targets for immunosuppression. Curr Opin Immunol. 2003; 15:479–486. [PubMed: 14499253]
31. Kondo T, Novick AC, Toma H, et al. Induction of chemokine gene expression during allogeneic skin graft rejection. Transplantation. 1996; 61:1750–1757. [PubMed: 8685955]
32. Miura M, El-Sawy T, Fairchild RL. Neutrophils mediate parenchymal tissue necrosis and accelerate the rejection of complete major histocompatibility complex-disparate cardiac allografts in the absence of interferon-gamma. Am J Pathol. 2003; 162:509–519. [PubMed: 12547709]
33. Miura M, Morita K, Kobayashi H, et al. Monokine induced by IFN-gamma is a dominant factor directing T cells into murine cardiac allografts during acute rejection. J Immunol. 2001; 167:3494–3504. [PubMed: 11544343]
34. Morita K, Miura M, Paolone DR, et al. Early chemokine cascades in murine cardiac grafts regulate T cell recruitment and progression of acute allograft rejection. J Immunol. 2001; 167:2979–2984. [PubMed: 11509648]
35. Amescua G, Collings F, Sidani A, et al. Effect of CXCL-1/KC production in high risk vascularized corneal allografts on t cell recruitment and graft rejection. Transplantation. 2008; 85:615–625. [PubMed: 18347542]
36. Beauregard C, Stevens C, Mayhew E, et al. Cutting edge: Atopy promotes Th2 responses to alloantigens and increases the incidence and tempo of corneal allograft rejection. J Immunol. 2005; 174:6577–6581. [PubMed: 15905494]
37. Flynn TH, Ohbayashi M, Ikeda Y, et al. Effect of allergic conjunctival inflammation on the allogeneic response to donor cornea. Invest Ophthalmol Vis Sci. 2007; 48:4044–4049. [PubMed: 17724186]
38. Hargrave SL, Hay C, Mellon J, Mayhew E, Niederkorn JY. Fate of MHC-matched corneal allografts in Th1-deficient hosts. Invest Ophthalmol Vis Sci. 2004; 45:1188–1193. [PubMed: 15037587]
39**. Niederkorn JY, Chen PW, Mellon J, et al. Allergic conjunctivitis exacerbates corneal allograft rejection by activating Th1 and Th2 alloimmune responses. J Immunol. 2010; 184:6076–6083. Clinicians have observed that patients with allergic conjunctivitis experience a steep increase in the risk for corneal allograft rejection. These prospective studies in a mouse model of ragweed pollen-induced allergic conjunctivitis confirm this suspicion and unexpectedly demonstrate that the increased risk for rejection is due to a systemic, rather than a local effect of the allergic conjunctivitis. Moreover, these studies also demonstrate the allergic diseases of mucosal, but not cutaneous tissues increase the incidence and tempo of graft rejection, which requires the joint participation of both Th1 and Th2 cells. [PubMed: 20410484]
40. Niederkorn JY, Chen PW, Mellon J, et al. Allergic airway hyperreactivity increases the risk for corneal allograft rejection. Am J Transplant. 2009; 9:1017–1026. [PubMed: 19422331]
41. Ghoraishi M, Akova YA, Tugal-Tutkun I, et al. Penetrating keratoplasty in atopic keratoconjunctivitis. Cornea. 1995; 14:610–613. [PubMed: 8575184]
42. Hargrave S, Chu Y, Mendelblatt D, et al. Preliminary findings in corneal allograft rejection in patients with keratoconus. Am J Ophthalmol. 2003; 135:452–460. [PubMed: 12654360]
43. Lyons CJ, Dart JK, Aclimandos WA, et al. Sclerokeratitis after keratoplasty in atopy. Ophthalmology. 1990; 97:729–733. [PubMed: 2197589]

44. Dahl ME, Dabbagh K, Liggitt D, et al. Viral-induced t helper type 1 responses enhance allergic disease by effects on lung dendritic cells. Nat Immunol. 2004; 5:337–343. [PubMed: 14973436]

45. Randolph DA, Stephens R, Carruthers CJ, et al. Cooperation between Th1 and Th2 cells in a murine model of eosinophilic airway inflammation. J Clin Invest. 1999; 104:1021–1029. [PubMed: 10525040]

46. Stern ME, Siemasko K, Gao J, et al. Role of interferon-gamma in a mouse model of allergic conjunctivitis. Invest Ophthalmol Vis Sci. 2005; 46:3239–3246. [PubMed: 16123425]

**Table 1**

Conditions that promote immune privilege of corneal allografts

| Condition | Mode of action | Effect on immune privilege |
|---|---|---|
| Absence of lymph vessels | Prevents APC migration to regional lymph nodes | Prevents induction of immune responses |
| FasL | Induces apoptosis of activated T cells at the graft–host interface | Blocks expression of immune responses |
| PD-L1 | Inhibits T cell proliferation and induces T cell apoptosis at the graft–host interface | Blocks expression of immune responses |
| ACAID | Suppresses DTH responses and deviates alloantibody responses to noncomplement-fixing isotypes | Prevents both induction and expression of immune responses |
| Tregs | Suppress immune responses | Prevent both induction and expression of immune responses |

ACAID, anterior chamber-associated immune deviation; DTH, delayed-type hypersensitivity; FasL, Fas ligand (CD95L); PD-L1, programmed death ligand 1; Tregs, T regulatory cells.



*Curr Opin Allergy Clin Immunol*. Author manuscript; available in PMC 2011 October 1.

**Table 2**

Factors that abolish immune privilege of corneal allografts

| Factor | Mode of action | Effect on alloimmune response |
|---|---|---|
| Lymph vessels in graft bed | Provide conduits for APC trafficking to regional lymph nodes | Promotes induction of alloimmune response |
| Blood vessels in graft | Elevation of chemokine expression | Promotes recruitment and activation of primed immune T cells into the corneal allograft |
| Mucosal allergic diseases | Unknown | Activates both Th1 and Th2 alloimmunity |
| Splenectomy | Prevents induction of ACAID | Prevents generation of ACAID Tregs |
| Depletion of γδ T cells | Prevents induction of ACAID | Prevents generation of ACAID Tregs |

ACAID, anterior chamber-associated immune deviation; APC, antigen-presenting cell; Tregs, T regulatory cells.