http://www-ermm.cbcu.cam.ac.uk

expert reviews in molecular medicine

Molecular mechanisms of immunity in corneal allotransplantation and xenotransplantation

Ying Qian and M. Reza Dana

Corneal allotransplantation is the most common and successful form of solid organ transplantation in humans. In uncomplicated cases, the two-year graft survival rate is over 90%. This extraordinary success can be attributed in part to various features of the normal cornea and anterior segment that together account for their 'immune-privileged' status. However, despite this success, a significant number of corneal grafts fail and immunological rejection remains by far the leading cause of graft failure. Studies on animal models of corneal transplantation have yielded a wealth of information on the molecular and cellular features of graft rejection, and have established that this process is mediated primarily by $CD4^+$ T cells of the T helper 1 (Th1) phenotype. In addition, studies have elucidated that certain facets of allosensitisation differ between corneal and other solid organ transplants. On the basis of these findings, novel experimental strategies selectively targeting the afferent or efferent arms of corneal alloimmunity have provided promising results in preventing corneal allograft rejection in the laboratory. Finally, because of the global shortage of human donor corneas, there is currently renewed interest in the possibility of using corneas from other species for transplantation into human eyes (xenotransplantation). Preliminary studies on animal models of corneal xenotransplantation have documented both antibody-mediated and cell-mediated responses that might play important roles in the accelerated rejection observed in corneal xenotransplants. This review synthesises the principal concepts emerging from studies of the molecular mechanisms in corneal transplant immunology.

Ying Qian, Postdoctoral Fellow, Laboratory of Immunology, Schepens Eye Research Institute, Harvard Medical School, 20 Staniford Street, Boston, MA 02114, USA. Tel: +1 617 912 7409; Fax: +1 617 912 0101; E-mail: yqian@vision.eri.harvard.edu

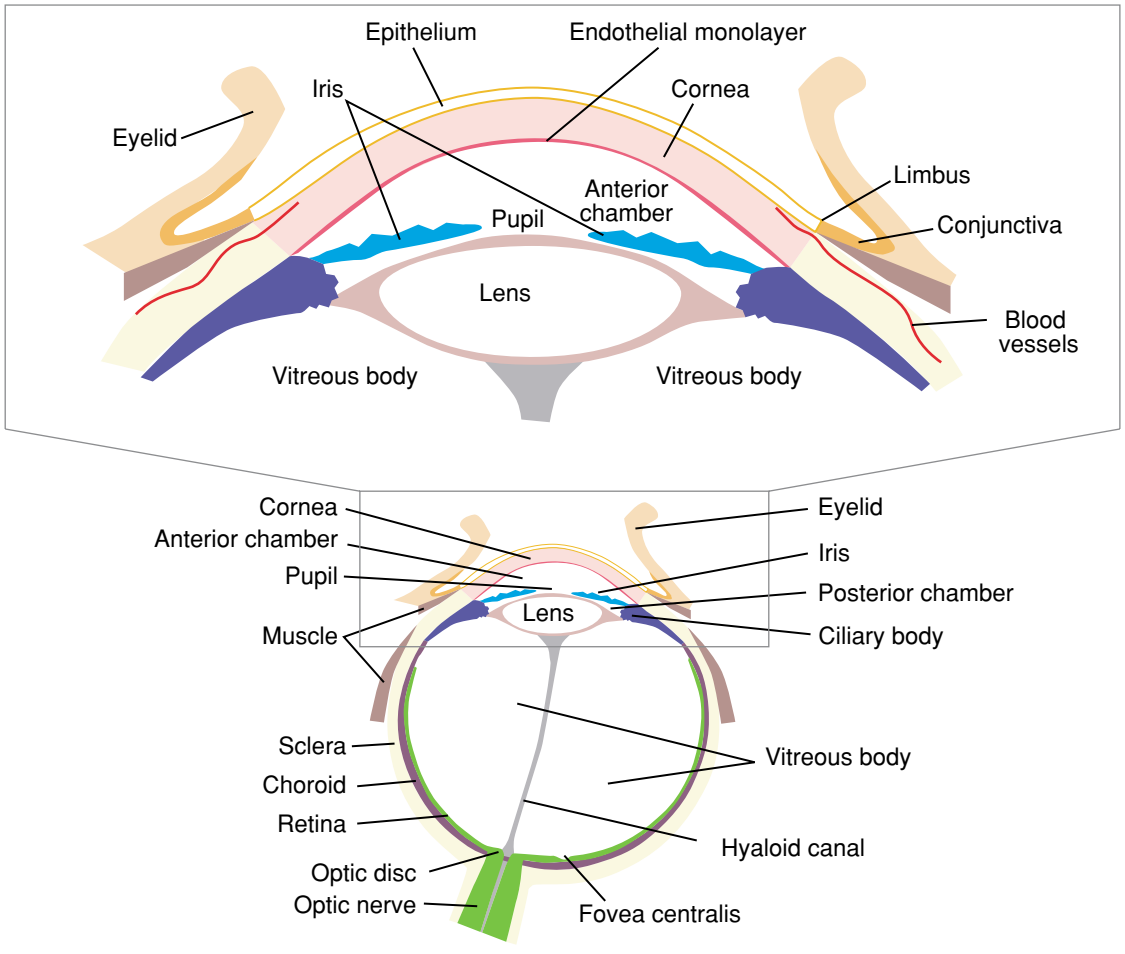
M. Reza Dana (corresponding author), Associate Professor, Laboratory of Immunology, Schepens Eye Research Institute, Harvard Medical School, 20 Staniford Street, Boston, MA 02114, USA. Tel: +1 617 912 7404; Fax: +1 617 912 0117; E-mail: dana@vision.eri.harvard.edu

Schepens Eye Research Institute website: http://www.eri.harvard.edu

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

https://doi.org/10.1017/S1462399401003246 Published online by Cambridge University Press

Corneal transplantation, which is also known as penetrating keratoplasty, is the most common form of tissue allotransplantation. In the USA alone, nearly 40 000 cases are performed annually. In uncomplicated first grafts, the two-year graft survival rate under cover of local immune suppression is over 90% (Ref. 1). This extraordinary rate of success, which can be achieved in other solid grafts only with profound systemic immune suppression, has been related to various features of the cornea and ocular microenvironment that together account for its immune-privileged status. First, expression of major histocompatibility complex (MHC) class II molecules is reduced or absent in the normal uninflamed cornea (Ref. 2). Second, the cornea secretes immunosuppressive factors that inhibit T-cell and complement activation (Refs 3, 4, 5). Third, the cornea [and other anterior chamber (AC) tissues – see Fig. 1] constitutively expresses Fas ligand (FasL, CD95L), which plays a pivotal role in protecting the eye from cell-mediated



Diagrammatic section of the eyeball, showing a close-up of the anterior segment

Figure 1. Diagrammatic section of the eyeball, showing a close-up of the anterior segment (fig001rdb).

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

damage. It is proposed that Fas$^+$ T cells, which enter the eye during inflammation, interact with FasL within the eye and are eliminated by apoptosis (programmed cell death) with no ensuing inflammatory damage. Consistent with this proposal, the eye of a *gld* (FasL-deficient) mouse appears to be unable to deter this damage and the corneal endothelium is targeted for immune-mediated destruction (Refs 6, 7, 8, 9, 10). Fourth, under normal uninflamed conditions, MHC class II$^+$ corneal Langerhans cells [LCs: a specific subset of antigen-presenting dendritic cells (DCs)] or other class II$^+$ 'professional' antigen-presenting cells (APCs) are rare in the cornea (Ref. 2). Finally, the cornea is avascular and devoid of lymphatics, which hinders traffic of immune elements between the eye and the lymphoid system.

The cornea is located in the immune-privileged AC. Allogeneic tissue (i.e. from an unrelated member of the same species) implanted into the AC survives for prolonged intervals of time compared with similar tissues implanted subcutaneously or at conventional, non-immune-privileged body sites (Ref. 11). This is a tolerogenic form of immunity in that the host becomes tolerant to intraocular antigens and fails to mount antigen-specific delayed-type hypersensitivity (DTH). Furthermore, this tolerance results in a selective and adoptively transferable suppression of antigen-specific DTH in the periphery known as AC-associated immune deviation (ACAID) (Refs 11, 12, 13, 14). This form of tolerance is not limited to naive hosts (who are later challenged with antigen); rather, even if the host is pre-sensitised to an antigen, ACAID can impose tolerance on this host (for its future interactions with antigen).

Immunological mechanisms of corneal allograft rejection

Although the cornea itself has been considered to be an immune-privileged tissue, many orthotopic corneal grafts (grafts placed in the normal anatomic location in recipients) are still rejected, and immune rejection is the leading cause of corneal graft failure (Ref. 1). Therefore, immune privilege is not absolute, and under circumstances that promote inflammation this privilege can be lost. One such setting is neovascularisation, which is a ubiquitous element of corneal pathology that can accompany a vast array of traumatic, inflammatory, infectious and toxic insults (Ref. 15). In corneal transplantation, corneal neovascularisation can significantly increase the risk of graft rejection as compared with the low-risk corneal transplant setting (i.e. first transplant into nonvascular and uninflamed hot beds). In fact, grafts placed into 'high-risk' beds exhibit rejection rates of 50–90%, even with maximal local and systemic immune suppression (Ref. 16). Therefore, the immune-privileged status of the cornea is abolished in these circumstances.

Humoral immunity

Cornea-specific and donor-specific antibodies have been detected in host serum after clinical (Refs 17, 18, 19) and experimental (Refs 20, 21) corneal grafting. However, these antibodies are not detected until after the grafts have been rejected (Ref. 21), and passive transfer of donor-specific antibodies fails to cause corneal allograft rejection in mice (Ref. 22). Moreover, clinical investigations in humans have shown that corneal allografts can undergo rejection in the absence of detectable donor-specific antibody (Ref. 18). Animals that are deficient in B cells (and are therefore unable to elicit antibody-mediated immunity) or the complement C3 component (and are therefore unable to use complement-fixing antibodies to promote rejection) consistently reject corneal grafts in a manner similar to their respective wild-type controls (Ref. 23). Thus, antibody production might be the result, rather than the cause, of corneal graft rejection in low-risk transplantation.

However, in clinical settings, corneal grafting often occurs in vascularised (high-risk) eyes. Post-transplant antibodies directed against donor MHC class I antigens in high-risk patients have been associated with graft rejection (Ref. 24). In addition, corneal grafts fare more poorly when transplanted into patients with pre-formed anti-class I antibodies as a consequence of previous corneal transplants or blood transfusions. Therefore, the human studies suggest that antibodies might in some instances contribute to graft failure if the recipient has been sensitised previously to donor antigens. However, it cannot be ruled out that the antibody response detected in corneal graft hosts is, at least in part, a byproduct of the cell-mediated (T-cell) response generated to the graft. A recent study on a murine model of high-risk corneal transplantation has provided supporting evidence for this notion (Ref. 25).

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

Cellular immunity

The two primary T-cell-dependent immune effector mechanisms that have been implicated in the rejection of solid tissue grafts are cytotoxic T lymphocyte (CTL) and DTH responses. CTLs are characterised by their expression of the CD8 cell-surface determinant, whereas cells mediating DTH typically express the CD4 surface marker. $CD4^+$ T helper (Th) cells can be further divided into two functional subsets, Th1 and Th2, which can be distinguished by the patterns of cytokines that they secrete. Th1 cells secrete interleukin 2 (IL-2), interferon γ (IFN-γ) and lymphotoxin, and are responsible for the development of the cell-mediated immune responses including DTH. Th2 cells secrete IL-4, IL-5, IL-10 and IL-13, and are responsible for promoting the production of high levels of IgG1, IgA and IgE by B cells (in mice), and for the activation of effector cells such as eosinophils (Ref. 26).

A large body of experimental evidence has established that corneal allograft rejection is a $CD4^+$ Th1-cell-mediated process. Corneal allograft rejection can be adoptively transferred with lymphocytes (Ref. 27), and in vivo depletion of $CD4^+$ T cells with anti-CD4 monoclonal antibodies (mAbs) leads to a significantly reduced incidence of corneal allograft rejection (Refs 28, 29, 30, 31), whereas treatment with anti-CD8 mAbs has no effect on the rejection rate of corneal allografts (Refs 28, 29). In addition, mice deficient in $CD4^+$ T cells are significantly impaired in their ability to reject orthotopic corneal allografts, whereas corneal allograft rejection proceeds unimpaired in mice deficient in $CD8^+$ T cells (Refs 32, 33). Reconstitution of severe combined immunodeficient (SCID) mice with $CD8^+$-depleted spleen cells leads to rejection rates similar to those of mice receiving undepleted spleen cells, whereas SCID mice reconstituted with $CD4^+$-depleted spleen cells display a significantly reduced rejection rate (Ref. 33). Moreover, rejection of corneal grafts correlates temporally better with recipient acquisition of donor-specific DTH rather than CTLs (Refs 34, 35, 36). Finally, the cytokine profile of cornea and aqueous humor in rejecting grafts is of the Th1 type (Refs 37, 38, 39).

Although $CD4^+$ Th1 cells have been shown to play the central role in most animal models of corneal graft rejection, some controversy still remains concerning the contribution of $CD8^+$ T cells in the rejection of allogeneic corneal grafts under certain circumstances. There are instances in which corneal allograft rejection is associated with the presence of CTLs (which are typically $CD8^+$ T cells) directed against donor-specific antigens. Allospecific CTLs are activated in mice receiving heterotopic corneal grafts (i.e. grafted at a site different from the normal anatomic position) (Refs 40, 41), rats receiving orthotopic corneal grafts (Refs 42, 43, 44, 45) and humans receiving corneal grafts (Refs 46, 47). However, studies using the murine model of orthotopic corneal transplantation have produced mixed results: some studies have suggested that CTLs do not play a role in corneal allograft rejection (Refs 28, 34, 48), whereas others indicate that CTLs mediate, at least in part, the alloresponse to minor H alloantigens (Ref. 49) and graft rejection in high-risk hosts (Refs 48, 50, 51). Subsequent studies in mice have demonstrated that $CD8^+$ T-cell-deficient or perforin-deficient hosts reject donor corneas mismatched for MHC and minor H antigens as effectively as do wild-type controls (Refs 33, 36), indicating that although $CD8^+$ T cells might be generated in response to corneal allografts, they do not play a crucial role in rejection of the corneal grafts. However, in some mice deficient in $CD4^+$ T cells, fully mismatched corneal allografts are rejected within 10 weeks of engraftment, undergoing delayed rejection after long-term acceptance. The $CD4^+$ T-cell knockout mice that have rejected allogeneic grafts do not generate significant DTH responses, suggesting a mechanism involving $CD8^+$ T cells in the late rejection of some corneal transplants (Refs 32, 33).

The afferent and efferent arm of corneal allograft rejection

The process of corneal transplant immunity can be conceptualized as being similar to the motor reflex induced in response to sensory stimulation, composed of an 'afferent' and an 'efferent' arm (Fig. 2). The afferent arm is synonymous with the process by which the graft host becomes sensitised to the donor antigens in the transplant (allorecognition). This requires processing of alloantigens by APCs (in particular, local DCs and LCs) and their successful presentation to naive T cells. Allorecognition itself can be further subdivided into discrete steps, including: (1) activation of APCs and their migration into the graft; (2) processing of antigens; and (3) presentation of antigens in the context of MHC

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

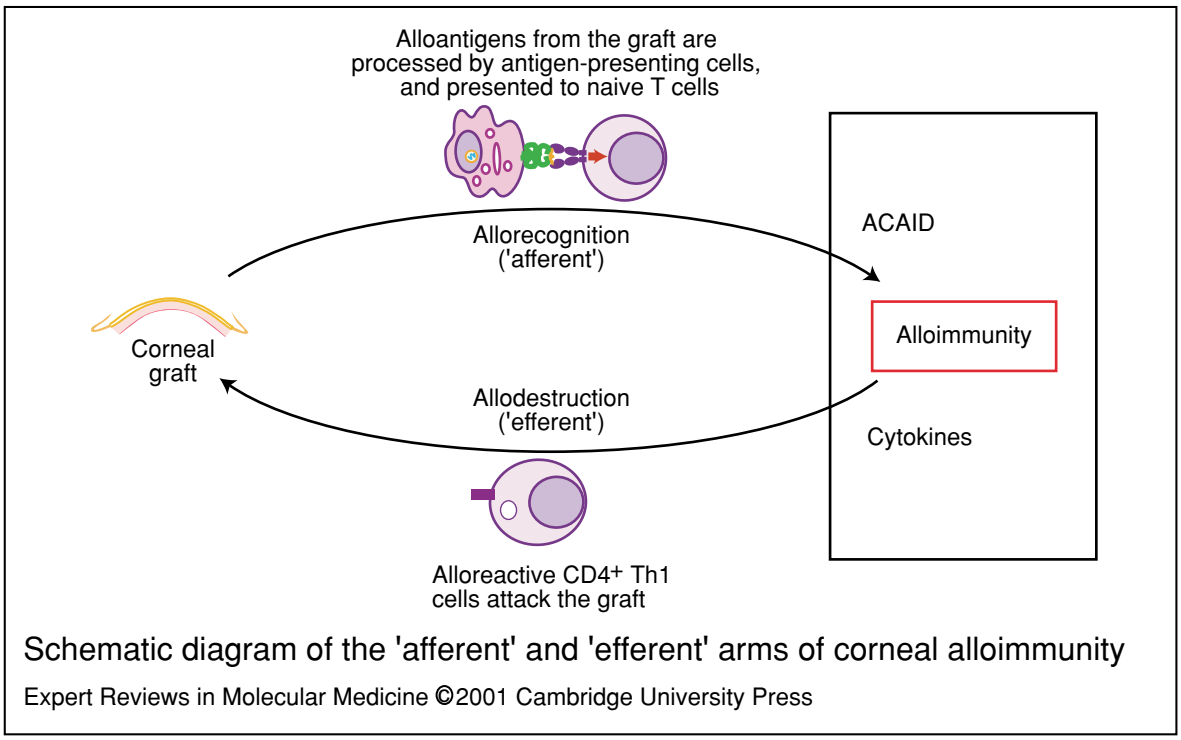


Figure 2. Schematic diagram of the 'afferent' and 'efferent' arms of corneal alloimmunity. Allorecognition and the allodestructive response can be considered synonymous with the afferent and efferent arms of the motor reflex that is induced in response to sensory stimulation. Both the afferent and efferent arms of the immune response generated to alloantigens are regulated by cytokines (see text for details) and by the anterior-chamber-associated immune deviation (ACAID) response. ACAID induces an antigen-specific response that is tolerising **(fig002rdb)**.

class II to the T-cell receptor (TCR) of naive T cells in the draining lymph node, which, together with adequate costimulation, results in T-cell activation (Refs 52, 53, 54, 55). The expression or efferent phase of the response is synonymous with the process of attacking the graft (the allodestructive response). This can likewise be divided into steps, consisting of: (1) entry of alloreactive T cells from lymphoid organs to the general circulation; (2) delivery of these cells to the target tissue and re-encounter with antigen; and, possibly, (3) development of 'memory', which might facilitate the expression of the alloimmune response if there is repeated exposure to antigen (Ref. 52). In the following sections, we discuss the cellular and molecular components that participate in the afferent and efferent arms of corneal allograft immunity.

Allorecognition of corneal alloantigens

Immunogenicity of each layer of the cornea

Theoretically, each layer of the cornea has the potential to contribute to the immunogenicity of this tissue as a graft. When corneal allografts are placed orthotopically in eyes of experimental animals, it is difficult to discern the immunogenic potential of the various layers because the graft is placed in an immune-privileged site (Refs 13, 56, 57). Therefore, a non-immune-privileged site, such as the space beneath the kidney capsule, can be helpful in testing the immunogenicity of each layer of the cornea. This approach has been used by transplantation immunologists to study the fate of various solid tissue grafts (Refs 58, 59, 60). When placed beneath the kidney capsule, allografts of mouse corneal epithelium, either alone or as stroma deprived of endothelium, undergo immune rejection and induce donor-specific DTH (Ref. 61). Such findings indicate that the alloimmunogenicity of the normal cornea largely resides within its epithelial and stromal layers.

The view that epithelium is the primary source of alloimmunogenicity in full-thickness mouse corneal grafts is consistent with a clinical study suggesting that human corneas deprived of

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

epithelium show better survival in keratoplasty (Ref. 62). However, a similar and subsequent study showed that the removal of epithelium does not reduce the likelihood of graft rejection (Ref. 63). The inconsistent results are explained in part by a recent study using a mouse model of corneal transplantation. Epithelium-deprived corneal grafts are swiftly rejected in allogeneic recipients because these allografts incite intense stromal inflammation and neovascularisation in the grafts and in the recipient beds. When epithelium-deprived corneal grafts are resurfaced with LC-deficient syngeneic epithelium, the composite corneal grafts are protected from immune rejection (Ref. 10). The findings indicate that, on the one hand, an intact epithelial layer inhibits the development of inflammation and neovascularisation within a graft by a mechanism that is unrelated to immunity, but, on the other hand, is potentially capable of promoting all forms of inflammatory responses including graft rejection.

Corneal alloantigens

In humans, the MHC is composed of human leukocyte antigens (HLAs) that include class I HLA-A, -B and -C, and class II HLA-DP, -DQ and -DR antigens. Initially, only class I HLA antigens were shown to be expressed on normal corneal epithelium and stromal cells but, later, class II HLA antigens were also found on DCs in the limbal epithelium and stroma, and on endothelial cells lining limbal blood vessels (Refs 64, 65, 66, 67). Despite well-established associations between the MHC and allograft rejection in other solid organ transplantation, there is considerable controversy about the role of MHC antigens in corneal transplantation. A beneficial effect of matching for HLA-A, -B and -DR antigens in clinical corneal transplantation has been observed in several prospective and retrospective studies, mainly in high-risk patients (Refs 68, 69, 70, 71). However, other studies, including the Collaborative Corneal Transplantation Studies (CCTS), do not show a significant effect on graft survival of HLA matching (Refs 72, 73, 74). Instead, results from the CCTS suggest that ABO blood group compatibility decreases the rejection rate in high-risk vascularised patients. Evidence from other studies also suggests that non-MHC antigens play an important role in clinical corneal allograft rejection (Ref. 75). Further studies evaluating the contribution of blood ABO antigens to clinical corneal alloimmunity are currently under way.

Experimental work using rats and mice has confirmed a prominent role for non-MHC antigens in corneal graft rejection. Orthotopic corneal allografts bearing minor H antigens alone are more likely to be rejected than are grafts displaying only MHC alloantigens (Refs 34, 51, 76). Although the chromosomal locations of several dozens of minor antigens have been determined in mice, the antigens themselves remain largely uncharacterised.

LCs and DCs

LCs are a population of constitutively immunogenic DCs that mediate antigen presentation and promote immune surveillance in the skin and ocular surface epithelium. As such, they play a critical role in allosensitisation. Corneal LCs are bone-marrow-derived cells that are thought to represent the professional APCs of the ocular surface and hence are capable of activating T cells and initiating ocular immune responses (Refs 77, 78). While MHC class II^+ LCs are physiologically absent from the central cornea (Ref. 2), several corneal stimuli (e.g. keratoplasty, trauma, infection and cauterisation) can induce centripetal (towards the centre) migration of LCs into the cornea from the limbus, where they might initiate antigen processing (Refs 79, 80, 81). The presence of LCs in the donor cornea has been shown to effect host allosensitisation and graft rejection (Refs 82, 83). Recent work in our laboratory (M.R. Dana et al., unpublished) has shown the presence of MHC class II^- resident DCs in the cornea. Inflammatory insults to the cornea lead to upregulation in the expression of class II antigens and costimulatory molecules (e.g. CD80, CD86) by these cells, thereby potentially rendering them capable of initiating T-cell responses. Hence, inflammation in the cornea can lead to enhanced presence of class II^+ APCs through two mechanisms: (1) recruitment of limbal LCs; and (2) upregulation of MHC class II on resident native LCs and other DCs.

Direct and indirect allosensitisation

T cells of the recipient can be activated directly by the donor APCs that present complexes of foreign donor MHC molecules and graft-derived peptides. This interaction, which is unique to the transplant situation, is referred to as direct recognition of alloantigens (Fig. 3). Alternatively,

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

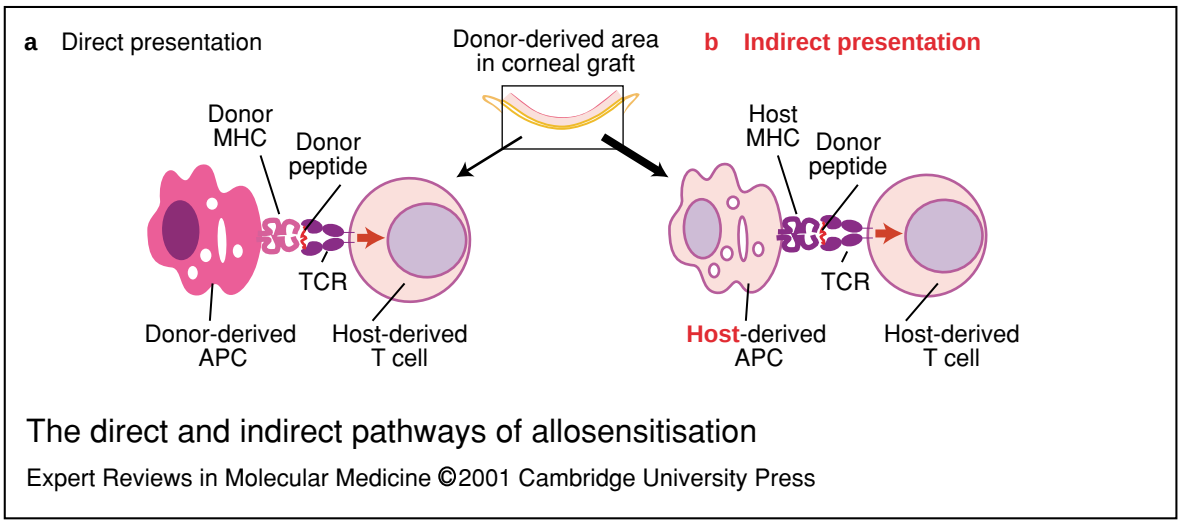


Figure 3. The direct and indirect pathways of allosensitisation. (a) In the direct pathway, major histocompatibility complex (MHC) molecules on donor antigen-presenting cells (APCs) from the graft tissue present graft-derived peptides to host T cells (TCR, T-cell receptor). (b) In the indirect pathway, host APCs take up graft proteins and present donor-derived processed peptides on host MHC to host T cells. The indirect pathway is thought to be the main route of sensitisation in corneal transplants, because constitutive MHC class II expression in donor tissue is low **(fig003rdb)**.

proteins shed from the graft are taken up and processed by the APCs of the recipient so the self-restricted Th cells are activated indirectly by recipient MHC class II molecules presenting graft-derived peptides (Fig. 3) (Refs 20, 84, 85).

In the typical form of organ transplantation, such as heart or kidney, the donor tissue contains significant numbers of 'passenger leukocytes' (e.g. APCs such as DCs/LCs) that express high levels of MHC class II and are highly motile, and hence can sensitise the host directly when T cells recognise the donor MHC (Ref. 86). This is different from the corneal graft setting, where there is very little expression of donor-type MHC and, as far as we know, virtually no class II^+ donor APCs in the graft tissue (Refs 87, 88). Despite our recent work (M.R. Dana et al., unpublished) showing the presence of MHC class II^- APCs (or DC precursors) in the cornea, the role of these cells in allorecognition remains unknown. What is known is that these cells are capable of upregulating class II expression after inflammation, as occurs in transplantation. Therefore, donor class II expression is present in the grafted tissue. Nevertheless, the relative paucity of constitutive expression of MHC class II in the donor tissue has led to the proposal that the indirect pathway of sensitisation is the dominant form of sensitisation. In this scenario, recipient APCs come into contact with graft-derived antigens, process them and present them in the context of host MHC to T cells – generating self-restricted or indirect alloreactive T cells (Refs 89, 90, 91). Streilein's group has reported that reactive T cells elicited in low-risk corneal grafting are largely self-restricted (Ref. 50). Furthermore, our laboratory has shown that suppression of host APCs (i.e. the indirect pathway) in the low-risk setting can lead to almost universal acceptance of grafts that are unmatched to the host with respect to minor and MHC antigens. This further underscores the relevance of the indirect pathway to host sensitisation to both donor MHC and minor antigens (Refs 92, 93). Therefore, a fundamental difference between low-risk corneal grafts and other solid transplants is that the immune response generated in low-risk corneal grafts is principally of the indirect, 'self-restricted' type.

However, multiple investigators have shown that, under appropriate stimulation (as might occur in inflamed corneal beds), expression of both class I and class II MHC antigens by corneal cells can be significantly upregulated (Refs 65, 94). Accordingly, under appropriate stimulation, particularly as might occur in the high-risk setting, resident corneal APCs might be capable of sensitising host T cells. Alternatively, enhanced expression of MHC might allow graft cells to serve as 'non-professional' APCs capable of peripheral

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

sensitisation. This might be possible given the high precursor frequency of cells responding to foreign (allo) MHC epitopes, and the highly probable enhanced localisation of recirculating T cells to high-risk neovascularised eyes. In summary, the indirect pathway appears to be the main mechanism of allosensitisation in the low-risk setting, but it is conceivable that the direct pathway might be important in the 'high-risk' setting.

Recruitment of effector cells to corneal allografts

Recruitment of inflammatory and immune cells to a tissue site represents the net functional effect of adhesion molecules and chemokines that function at the level of the vascular endothelium as well as the tissue matrix (Refs 95, 96). Research over the past five years has thoroughly described the steps in the generation of a cell-mediated immune response and related these to specific chemokine responses: APC traffic to the site of inflammation, migration of activated APCs to secondary lymphoid organs, colocalisation of APCs with naive T cells for priming, selective generation of Th1/Th2 polarised T-cell clones, and transendothelial migration and homing of T cells to the target organ (Fig. 4) (Refs 96, 97, 98). Major stimuli for adhesion molecule and inducible chemokine expression include the pro-inflammatory cytokines IL-1 and tumour necrosis factor α (TNF-α) (Refs 95, 96, 98), as well as bacterial products such as endotoxin (Ref. 96).

When chemokines were first described more than a decade ago, many products were shown to be upregulated in response to pro-inflammatory cytokines. This led to a dilemma: if ubiquitous pro-inflammatory cytokines stimulate secretion of a wide array of chemokines, how can the subsequent chemokine response retain selectivity? The answer is twofold: chemokines do not act alone, but function in concert with other molecular mediators including integrins and other adhesion factors; and, importantly, the type

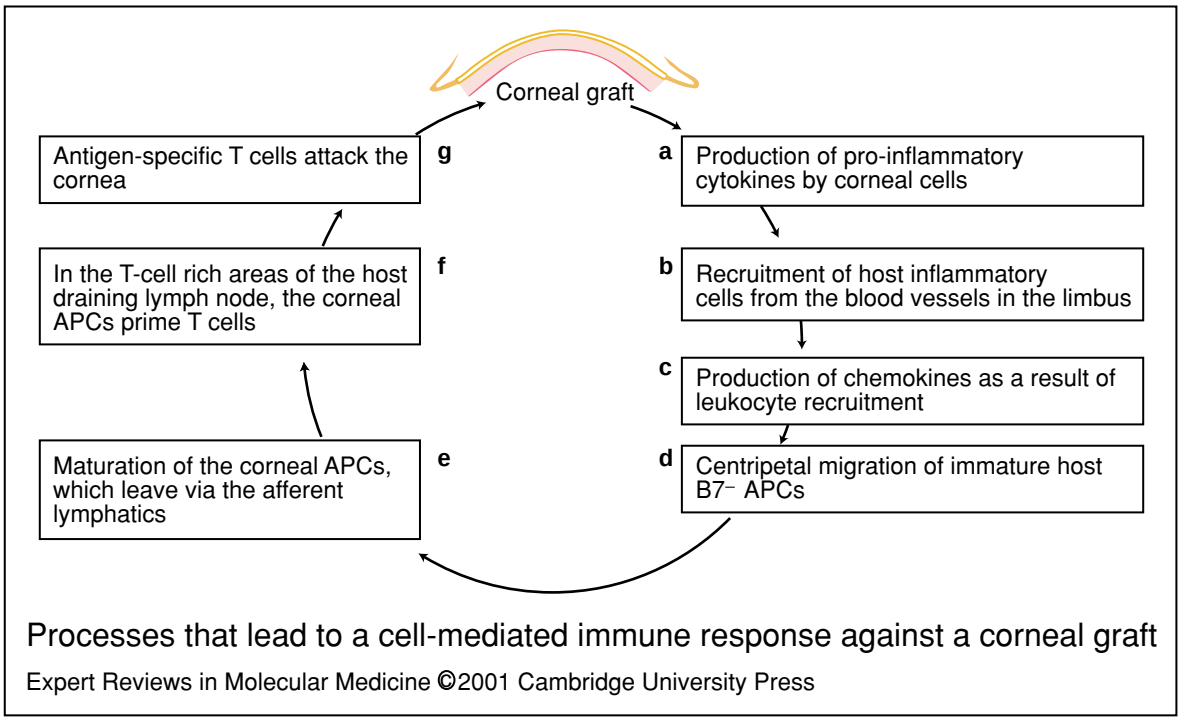


Figure 4. Processes that lead to a cell-mediated immune response against a corneal graft. (a) Production of pro-inflammatory cytokines in the cornea as a result of grafting leads to (b) recruitment of host inflammatory cells (mostly polymorphonuclear neutrophils) from the limbal vasculature. (c) Leukocyte recruitment in the cornea results in the production of chemokines, which (d) induces centripetal migration of immature ($B7^-$) antigen-presenting cells (APCs), such as Langerhans cells. (e) After maturation, these APCs leave the cornea by entering afferent lymphatics, thereby gaining access to draining lymph nodes. (f) The APCs converge in the parafollicular T-cell-rich areas of the lymph node, where they prime T cells. (g) The final, effector phase of the immune response involves the targeting of the cornea by antigen-specific primed $CD4^+$ T cells **(fig004rdb)**.

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

and degree of leukocytic response generated is controlled largely by the specific subgroup of chemokine receptors expressed by specific cell types (Refs 96, 97, 98, 99). For example, expression of IFN-γ and IL-12, which are critical cytokines involved in the development of DTH responses, is associated with selective expression of chemokine receptors CCR1, CCR5 and CXCR3 by T-cell subsets. This leads to localisation of Th1 cells to sites of DTH expression, such as allograft rejection (Refs 99, 100, 101, 102, 103).

Chemokine biology is starting to attract more attention from transplantation immunologists, particularly since upregulation of select CC chemokines has been related to rejection of human kidney (Refs 104, 105) and rodent heart (Ref. 106) grafts. Recently, the differential gene expression of chemokines in experimental corneal transplant rejection has been reported (Ref. 107). Although many aspects of the chemokine biology of corneal transplantation remain unknown, there is now firm evidence to suggest that select chemokines of the CXC (α) and CC (β) families are associated with basic cellular mechanisms involved in corneal allograft rejection. Specifically, it has been shown that there is overexpression of RANTES (for 'regulated on activation normal T-cell expressed and secreted'), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, MIP-2 and monocyte chemotactic protein 1 (MCP-1) in eyes with rejected allografts. In addition, the data suggest high levels of gene transcription for the IFN-γ-inducible protein IP-10 in recipients prone to rejection. It is anticipated that increased understanding of the role of chemokines and chemokine receptors in corneal transplantation biology will open new doors for the development of molecular strategies for immune modulation in corneal transplant rejection. For example, our laboratory has recently discovered (M.R. Dana et al., unpublished) that selective antagonism of the chemokine receptor CCR1 leads to a dramatic increase in the survival of corneal allografts.

Immune modulation

Current immunosuppressive drugs used to prevent or treat corneal graft rejection in humans include corticosteroids and cyclosporin A. However, corticosteroids are only variably effective in either the prevention or treatment of high-risk corneal graft rejection, and their use sometimes results in cataracts, glaucoma and opportunistic infections (Refs 73, 108). While several investigators have been strong proponents of systemic cyclosporin use, the efficacy of this agent in the high-risk setting is far from clear, as demonstrated recently by a double-masked prospective trial in the UK (Ref. 109). Moreover, systemic immunosuppressive agents are fraught with a myriad of risks since they induce nonspecific suppression of both acquired and innate immunity (Refs 28, 110, 111, 112). Recently, a number of laboratories have had success in promoting transplant survival in rodent models of corneal transplantation, as described below (see also Table 1). However, it should be noted that the clinical applicability of these specific promising strategies remains to be tested in clinical trials.

Prevention of corneal graft rejection by inhibiting the afferent arm of alloimmunity

Inhibition of LC migration

The migration of LCs into corneal grafts is regulated, at least partly, by the pro-inflammatory cytokines IL-1 and TNF-α. IL-1 is a potent pro-inflammatory cytokine produced primarily by monocytes and macrophages, but also by resident corneal cells (Refs 113, 114). This cytokine has a wide range of activities, including mediation of the acute-phase response, induction of chemotaxis and activation of inflammatory cells and APCs, and stimulation of neovascularisation (Refs 115, 116, 117). IL-1 receptor antagonist (IL-1Ra) is a naturally occurring IL-1 isoform produced by the same cells that synthesise IL-1. It undergoes high-affinity binding to IL-1 receptors, but shows no agonist activity (Refs 118, 119, 120). Intracorneal injection of IL-1 induces centripetal migration of peripheral LCs (Refs 121, 122). Conversely, neutralising the activity of IL-1 by topical administration of IL-1Ra leads to a profound suppression of inflammation-induced LC migration in the cornea (Ref. 55), and a significantly reduced level of infiltrating host LCs in both low-risk and high-risk corneal grafts (Ref. 93).

TNF-α mediates many pro-inflammatory and immune-regulatory functions, such as upregulation of the expression of adhesion and costimulatory molecules, activation of neutrophils, induction of chemokine secretion, and activation of the NF-κB signal transduction pathway (Refs 115, 123). In the cornea, significant expression of TNF-α by the corneal resident

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

Table 1. Potential strategies for immune modulation to promote corneal transplant survival (tab001rdb)

Alloimmunity and rejection process targeted	Experimental immune modulation	Refs
Maturation of resident corneal (donor) APCs	Targeting cytokines IL-1 and TNF-α Targeting CD40 on T cells	54, 55, 93, 130
APC migration from host rim to graft	Targeting chemokine receptor CCR5 Targeting cytokines IL-1 and TNF-α	55, 92, 93, 122, 130, 178
Migration of APCs into afferent lymphatics	?Modulation of lymphoangiogenesis or lymphatic growth factors (VEGF-c)	
Interaction between APCs and naive T cells	Targeting costimulatory pathway of T-cell activation (CD40–CD154)	39
Th1 differentiation	Overexpression of Th2 cytokines Oral tolerance	44, 135, 141, 163, 164, 165
Trafficking of effector cells to the graft	Suppression of adhesion molecules Angiostatic strategy	145, 146, 147, 148, 153, 154
Destruction of corneal allograft	?Anti-apoptosis strategy	

Abbreviations: APC, antigen-presenting cell; IL-1, interleukin 1; TNF-α, tumour necrosis factor α; VEGF, vascular endothelial growth factor.

cells can be induced by inflammatory stimuli (Ref. 124). TNF-α activity is regulated by two distinct receptors: the type I receptor (p55; TNFR-I) and the type II receptor (p75; TNFR-II), which have largely homologous extracellular domains but distinct intracellular domains that can mediate discrete cellular responses (Ref. 125). TNFR-I is believed to be the principal receptor through which many of the pro-inflammatory activities of TNF-α are mediated (Refs 126, 127). The bioactivity of TNF-α can be dramatically suppressed by soluble TNFR-I, which binds free TNF-α and prevents ligation of the membrane-bound receptors (Ref. 128). Administration of TNF-α by intracorneal injection not only induces migration of LCs into the central cornea but also leads to a marked increase in the number of recruited LCs at the corneal limbus, which serves as a potential reservoir for corneal LCs. In gene-targeted knockout mice lacking TNFR-I or TNFR-II, the migratory response of LCs to thermal cautery or cytokine stimulation is profoundly attenuated (Ref. 122). Our recent work (M.R. Dana et al., unpublished) suggests that IL-1 and TNF-α mediate the recruitment of native DCs (including LCs) through upregulation of select chemokines (e.g. RANTES, MIP-1β) and chemokine receptors (e.g. CCR5). Consistent with this, CCR5 knockout mice exhibit a significantly decreased propensity for LC recruitment to the cornea.

On the basis of the experimental data above, IL-1 and TNF-α as well as downstream chemokines induced by these cytokines provide targets for therapeutic intervention in the prevention of corneal allograft rejection. Indeed, the concurrent overexpression of IL-1 and TNF-α has been reported in corneal transplantation (Ref. 129). Inhibition of IL-1 activity by topical IL-1Ra successfully prolongs both low- and high-risk orthotopic corneal allografts in the mouse (Ref. 54). The enhanced graft survival is associated with suppressed allosensitisation, as demonstrated by a lack of DTH response to donor alloantigens in treated animals (Ref. 93). In addition, mice with a gene-targeted deficiency in TNFR-I accept grafts disparate in minor H antigens at a significantly higher rate than do wild-type controls (Ref. 92). A subsequent study has further demonstrated that neutralisation of TNF-α activity by topical administration of soluble TNFR-I promotes the acceptance of allogeneic corneal transplants in mice (Ref. 130).

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

Blockade of costimulatory pathways

T-cell activation requires the interaction of the TCR with the MHC–peptide complex on the APC (signal 1) as well as requisite costimulatory signals (signal 2) provided by the APC. One of the major signalling pathways responsible for delivery of this costimulatory signal is the interaction of CD28 on T cells with B7 molecules found on APCs (Ref. 131). A recombinant immunoglobulin (Ig) fusion protein, CTLA-4–Ig, comprising CTLA-4 and the CH2 and CH3 domains of human IgG, binds B7 with high affinity and prevents its interaction with CD28 (Ref. 132). Prolonged survival of corneal allografts has been achieved using CTLA-4–Ig as a blocking agent in animal models. Postoperative systemic administration of CTLA-4–Ig prolongs the mean survival of corneal allografts from 14 days to 24 days in mice (Ref. 133). Furthermore, incubation of rabbit donor corneas with CTLA-4–Ig prior to transplantation enhances allograft survival in vascularised high-risk recipients, but not in avascular low-risk recipients (Ref. 134). A recent study delivered vectors containing the gene encoding CTLA-4 to donor corneal epithelium and reported prolonged corneal graft survival using this approach (Ref. 135).

Another critical costimulatory signal for T-cell activation is the CD40–CD154 pathway, which can activate both B7 and IL-12 expression by APCs. The net effect of CD40 ligation on $CD4^+$ T cells is their differentiation down the Th1 pathway (Ref. 136). Blockade of the CD40–CD154 interaction by anti-CD154 mAb has been shown to prevent rejection of non-ocular solid organ allografts, such as cardiac, renal, pancreatic islet, and skin grafts (Refs 137, 138, 139). Similarly, systemic treatment with anti-CD154 mAb promotes universal acceptance of corneal transplants, regardless of the degree of allodisparity or preoperative risk (Ref. 39).

Overexpression of Th2 cytokines

As described above, the rejection of orthotopic corneal allografts is principally a consequence of the actions of $CD4^+$ T cells of the Th1 type, which secrete IFN-γ and IL-2. However, Th1 cells are cross-regulated by $CD4^+$ T cells of the Th2 type, which secrete IL-4 and IL-10. The cytokines produced by Th2 cells suppress the activation and release of cytokines from Th1 cells, thereby limiting the ability of the latter cells to mediate immune responses such as DTH (Ref. 140). When the immune system of adult mice is biased towards the Th2 response by immunisation with keyhole limpet haemocyanin (KLH) and incomplete Freund's adjuvant (IFA), the mice accept subsequent orthotopic corneal allografts at a higher rate than do normal mice. Moreover, the Th2-biased mice fail to acquire donor-specific, allodestructive $CD4^+$ T cells that secrete IFN-γ and mediate DTH (Ref. 141). Consistently, transfection with the Th2 cytokine IL-4 of donor corneal epithelium prolongs corneal graft survival in comparison with controls (Ref. 135).

Prevention of corneal graft rejection by suppressing the efferent arm of alloimmunity

Inhibition of adhesion molecules

Graft invasion by recipient effector cells is mediated by cell adhesion molecules that are detected readily at sites of corneal immune inflammation (Refs 142, 143, 144). Systemic treatment of mice with mAbs to intercellular adhesion molecule 1 (ICAM-1), leukocyte function-associated antigen 1 (LFA-1) or very late antigen 4 (VLA-4) has shown promising results in enhancing corneal allograft survival (Refs 145, 146, 147, 148). The prolonged graft survival is associated with suppressed levels of the Th1 cytokines IFN-γ and IL-2 in treated hosts (Ref. 149). However, two studies have indicated that LFA-1 and ICAM-1 are involved in recipient sensitisation to alloantigens rather than in the allodestructive effector phase (Refs 95, 147).

Reduction of corneal neovascularisation

Neovascularisation is a ubiquitous element of corneal pathology that can accompany a vast array of infectious, inflammatory, traumatic and toxic insults (Refs 53, 150, 151). It has been shown in both human (Ref. 152) and mouse (Ref. 76) settings that corneal transplantation alone can induce neovascularisation. Because postkeratoplasty corneal neovascularisation likely facilitates the recruitment of immune cells, and therefore the expression of immune and inflammatory responses in the graft site, reduction of this process (angiostasis) might improve the outcome of corneal transplantation. Topically neutralising the activity of vascular endothelial growth factor (VEGF), a potent angiogenic cytokine (Ref. 153), prolongs corneal allograft

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

survival and is associated with suppressed transplantation-induced corneal neovascularisation and reduced infiltrating cells in the grafts (Ref. 154).

Prevention of corneal graft rejection by inducing allospecific tolerance

Induction of allospecific ACAID

ACAID is a tolerogenic form of immunity that is induced in response to intraocular antigens and that leads to a selective and adoptively transferable suppression of antigen-specific DTH in the periphery (Ref. 15). ACAID has been elicited by a wide range of different types of antigens, including alloantigens. Implantation of allogeneic spleen (Refs 35, 155, 156), peritoneal exudate cells (Ref. 157), corneal epithelial and endothelial cells (Ref. 156), or segments of allogeneic corneal tissue (Ref. 158) into the AC of mouse eyes induces ACAID. Recipients of these cells or fragments fail to develop donor-specific DTH. More importantly, induction of donor-specific ACAID by these donor cells effectively prolongs the survival of subsequent orthotopic corneal grafts (Refs 35, 155, 156, 157). Accordingly, implantation of fragments of allogeneic corneal tissue in the AC of the host eye (which is capable of efficiently inducing ACAID) reduces the risk of rejection in subsequent orthotopic corneal allografts (Refs 156, 159).

Oral tolerance

Oral antigen administration is an effective tolerising regimen for desensitising previously immunised hosts (Ref. 160) and for downregulating the immune response to a variety of antigens, including alloantigens (Refs 161, 162). Oral administration of cultured corneal epithelial and endothelial cells obtained from donors results in a 50% reduction in graft rejection in mice (Refs 44, 163). This graft enhancement can be augmented by conjugating the oral cell inoculum with the nontoxic B subunit of the mucosal adjuvant cholera toxin (Ref. 164). Importantly, orally induced graft enhancement is alloantigen specific, and third-party corneal allografts (donor corneal tissue obtained from mice that are of a different strain from both the immunised recipients and the donors used for preparing the corneal cells for immunisation) are not affected by oral antigen administration (Ref. 165).

Corneal xenotransplantation

General concepts of xenotransplantation

Xenogeneic transplantation is the transplantation of tissues from a member of one species to that of another. Potential xenogeneic donors can be subdivided into 'discordant' donors, against whose tissues the recipient possesses pre-formed xenoreactive natural antibodies (NAbs), and 'concordant' donors, against whose tissues such NAbs are absent (Ref. 166). Primate species concordant with human recipients are considered unlikely candidates as donors of xenogeneic tissues for a variety of practical and ethical reasons. The possibility of using discordant tissue sources for xenotransplantation is, then, of considerable interest (Refs 167, 168).

Xenografts are always rejected faster than allografts when similar types of tissues are transplanted under similar circumstances. The barriers to success of xenografts significantly exceed the barriers to success of allografts. Xenotransplantation of vascularised organs, such as kidney and heart, in discordant donor–host combinations invariably results in hyperacute antibody-mediated rejection within minutes or hours. The rapidity of rejection is generally thought to be mediated by pre-existing NAbs via activation of complement components (Refs 169, 170).

Immunity of corneal xenotransplants

Although keratoplasty is readily available in the USA and in certain other regions of the developed world, the need for human donor corneas far exceeds supply on a worldwide scale (Ref. 171). In addressing this shortage, animal cornea might be a substitute. Because the cornea is an immune-privileged tissue, its fate as a xenograft might be different from, and perhaps even better than, that of other types of solid tissue xenografts. Fragments of guinea pig cornea implanted in the AC (an immune-privileged site) of normal mouse eyes survive for prolonged intervals of time, and many grafts retain clarity and display little evidence of immune rejection during an 8-week observation period (Ref. 172). Xenogeneic antigens expressed on corneal fragments in the AC of mouse eyes evoke no change in recipient humoral immune status and induce mild guinea-pig-specific DTH (Ref. 173). These findings indicate that immune privilege in the AC is extended to xenogeneic corneal tissue.

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

Although the fate of intracameral (contained in the AC) corneal xenografts is good, xenografts of this type survive poorly when placed orthotopically in eyes of normal rats or mice. Guinea pig to rat orthotopical xenografts have been reported to survive for relatively short periods (3–8 days) (Refs 174, 175, 176). The presence of anti-donor pre-formed antibodies to leukocytes in all recipients and the deposition of rat IgG2a, IgG1 and IgM on the grafts are consistent with early antibody- and complement-mediated damage. The early graft damage is followed at 7–14 days by evidence of a cell-mediated response, involving the infiltration of substantial numbers of activated $CD4^+$ cells and fewer $CD8^+$ cells, macrophages and granulocytes into the graft, as well as the prominent infiltration of eosinophils at the host–graft interface (Refs 175, 176). In addition to immune effector mechanisms, experimental xenotransplantation has been complicated by technical difficulties of grafting corneas among different species (size and thickness disparity), so that loss of corneal xenografts in some cases results from experimental rather than immune variables.

Taken together, studies on models of guinea pig to mouse orthotopic transplantation do not suggest an important antibody-mediated rejection mechanism. Guinea pig to mouse orthotopic xenografts are rejected acutely (between 8 and 16 days), but not hyperacutely (less than 3 days), in eyes of normal BALB/c and C57BL/c mice (Ref. 177). Since the cornea is an avascular tissue, hyperacute rejection, which results from vascular occlusion and is commonly seen in vascularised solid organ xenografts, is not seen in corneal xenografts. The survival of cornea xenografts in mice genetically deficient both in B cells and antibody formation is virtually identical to that in wild-type mice. However, acute rejection is avoided by guinea pig grafts placed in the eyes of CD4-knockout mice, and reconstitution of these mice with normal $CD4^+$ T cells restores the capacity for rejection. Therefore, the experimental evidence in murine xenotransplantation indicates that $CD4^+$ T cells, rather than antibodies, are the primary mediators of acute corneal xenograft rejection in the discordant combination with mice as recipients.

Conclusions

Studies on the immunobiology of corneal xenografts are still at an early stage. The differential fate of intracameral versus orthotopical corneal xenografts, the speed of rejection of orthotopic corneal xenografts, and the involvement of humoral and/or cell-mediated immune responses in corneal xenograft rejection are general worthy areas for further investigation. Exploiting these areas might lead to knowledge that can improve the fate of orthotopic corneal xenografts, such that these could be offered as an alternative to allotransplantation to patients in need of corneal grafts.

Acknowledgements and funding

We acknowledge the constructive peer review of this manuscript by Professors J. Wayne Streilein and Andrew Taylor (Schepens Eye Research Institute, Harvard Medical School, Boston, MA, USA). Our work is supported by National Institute of Health Grant NEI12963, Biogen, Eye Bank Association of America, Research to Prevent Blindness, and Fight for Sight.

References

1 Rocha, G., Deschenes, J. and Rowsey, J.J. (1998) The immunology of corneal graft rejection. Crit Rev Immunol 18, 305-325, PubMed ID: 98369815

2 Streilein, J.W., Toews, G.B. and Bergstresser, P.R. (1979) Corneal allografts fail to express Ia antigens. Nature 282, 326-327, PubMed ID: 80054734

3 Jager, M.J., Bradley, D. and Streilein, J.W. (1995) Immunosuppressive properties of cultured human cornea and ciliary body in normal and pathological conditions. Transpl Immunol 3, 135-142, PubMed ID: 96103422

4 Nishida, K. et al. (1995) Transforming growth factor-beta 1, -beta 2 and -beta 3 mRNA expression in human cornea. Curr Eye Res 14, 235-241, PubMed ID: 95317076

5 Taylor, A.W. (1996) Neuroimmunomodulation in immune privilege: role of neuropeptides in ocular immunosuppression. Neuroimmunomodulation 3, 195-204, PubMed ID: 97248212

6 Griffith, T.S. et al. (1995) Fas ligand-induced apoptosis as a mechanism of immune privilege. Science 270, 1189-1192, PubMed ID: 96072969

7 Wilson, S.E. et al. (1996) The Fas-Fas ligand system and other modulators of apoptosis in the cornea. Invest Ophthalmol Vis Sci 37, 1582-1592, PubMed ID: 96295375

8 Stuart, P.M. et al. (1997) CD95 ligand (FasL)-

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

induced apoptosis is necessary for corneal allograft survival. J Clin Invest 99, 396-402, PubMed ID: 97174338
9 Yamagami, S. et al. (1997) Role of Fas-Fas ligand interactions in the immunorejection of allogeneic mouse corneal transplants. Transplantation 64, 1107-1111, PubMed ID: 98015901
10 Hori, J. and Streilein, J.W. (2001) Role of recipient epithelium in promoting survival of orthotopic corneal allografts in mice. Invest Ophthalmol Vis Sci 42, 720-726, PubMed ID: 21125409
11 Streilein, J.W. (1993) Tissue barriers, immunosuppressive microenvironments, and privileged sites: the eye's point of view. Reg Immunol 5, 253-268, PubMed ID: 94198139
12 Niederkorn, J.Y. (1999) The immune privilege of corneal allografts. Transplantation 67, 1503-1508, PubMed ID: 99328181
13 Niederkorn, J.Y. (1990) Immune privilege and immune regulation in the eye. Adv Immunol 48, 191-226, PubMed ID: 90273896
14 Streilein, J.W. (1999) Immunologic privilege of the eye. Springer Semin Immunopathol 21, 95-111, PubMed ID: 99386034
15 Epstein, R.J. et al. (1987) Corneal neovascularization. Pathogenesis and inhibition. Cornea 6, 250-257, PubMed ID: 88081670
16 Mader, T.H. and Stulting, R.D. (1991) The high-risk penetrating keratoplasty. Ophthalmol Clin North Am 4, 411-426
17 Ehlers, N., Olsen, T. and Johnsen, H.E. (1981) Corneal graft rejection probably mediated by antibodies. Acta Ophthalmol (Copenh) 59, 119-125, PubMed ID: 81156222
18 Smiddy, W.E. et al. (1986) Clinical and immunological results of corneal allograft rejection. Ophthalmic Surg 17, 644-649, PubMed ID: 87091014
19 Jager, M.J. et al. (1991) Cellular and humoral anticorneal immune response in corneal transplantation. Arch Ophthalmol 109, 972-977, PubMed ID: 91291067
20 Hutchinson, I.V., Alam, Y. and Ayliffe, W.R. (1995) The humoral response to an allograft. Eye 9, 155-160, PubMed ID: 96014777
21 Treseler, P.A. and Sanfilippo, F. (1985) Humoral immunity to heterotopic corneal allografts in the rat. Transplantation 39, 193-196, PubMed ID: 85116538
22 Hedge, S. et al. (1998) Antibody- and cell-mediated immune responses during rejection of a murine orthotopic corneal graft [ARVO Abstract]. Invest Ophthalmol Vis Sci 39, S455
23 Goslings, W.R. et al. (1999) Corneal transplantation in antibody-deficient hosts. Invest Ophthalmol Vis Sci 40, 250-253, PubMed ID: 99103527
24 Hahn, A.B. et al. (1995) The association of lymphocytotoxic antibodies with corneal allograft rejection in high risk patients. The Collaborative Corneal Transplantation Studies Research Group. Transplantation 59, 21-27, PubMed ID: 95141361
25 Hargrave, S.L. et al. (2000) High-risk corneal allografts are capable of stimulating complement dependent cytolytic antibodies. Cornea 19, 521-525, PubMed ID: 20382515
26 Morel, P.A. and Oriss, T.B. (1998) Crossregulation between Th1 and Th2 cells. Crit Rev Immunol 18, 275-303, PubMed ID: 98369814
27 Khodadoust, A.A. and Silverstein, A.M. (1976) Induction of corneal graft rejection by passive cell transfer. Invest Ophthalmol 15, 89-95, PubMed ID: 76094266
28 He, Y.G., Ross, J. and Niederkorn, J.Y. (1991) Promotion of murine orthotopic corneal allograft survival by systemic administration of anti-CD4 monoclonal antibody. Invest Ophthalmol Vis Sci 32, 2723-2728, PubMed ID: 91373112
29 Ayliffe, W. et al. (1992) Prolongation of rat corneal graft survival by treatment with anti-CD4 monoclonal antibody. Br J Ophthalmol 76, 602-606, PubMed ID: 93041587
30 Pleyer, U. et al. (1995) Effect of topically applied anti-CD4 monoclonal antibodies on orthotopic corneal allografts in a rat model. Invest Ophthalmol Vis Sci 36, 52-61, PubMed ID: 95122330
31 Coupland, S.E. et al. (1995) Delay in corneal allograft rejection due to anti-CD4 antibody given alone and in combination with cyclosporin A and leflunomide. Ger J Ophthalmol 4, 294-301, PubMed ID: 96077657
32 Yamada, J., Kurimoto, I. and Streilein, J.W. (1999) Role of CD4+ T cells in immunobiology of orthotopic corneal transplants in mice. Invest Ophthalmol Vis Sci 40, 2614-2621, PubMed ID: 99437356
33 Haskova, Z. et al. (2000) CD4+ T cells are critical for corneal, but not skin, allograft rejection. Transplantation 69, 483-487, PubMed ID: 20170372
34 Joo, C.K, Pepose, J.S. and Stuart, P.M. (1995) T-cell mediated responses in a murine model of

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

orthotopic corneal transplantation. Invest Ophthalmol Vis Sci 36, 1530-1540, PubMed ID: 95325104
35 Yao, Y.F. et al. (1997) Correlation of anterior chamber-associated immune deviation with suppression of corneal epithelial rejection in mice. Invest Ophthalmol Vis Sci 38, 292-300, PubMed ID: 97192869
36 Hegde, S. and Niederkorn, J.Y. (2000) The role of cytotoxic T lymphocytes in corneal allograft rejection. Invest Ophthalmol Vis Sci 41, 3341-3347, PubMed ID: 20463116
37 Yamagami, S. et al. (1998) Cytokine profiles of aqueous humor and graft in orthotopic mouse corneal transplantation. Transplantation 66, 1504-1510, PubMed ID: 99084437
38 Sano, Y. et al. (1998) Cytokine expression during orthotopic corneal allograft rejection in mice. Invest Ophthalmol Vis Sci 39, 1953-1957, PubMed ID: 98394402
39 Qian, Y. et al. (2001) Blockade of CD40-CD154 costimulatory pathway promotes survival of allogeneic corneal transplants. Invest Ophthalmol Vis Sci 42, 987-994, PubMed ID: 11349110
40 Peeler, J., Niederkorn, J. and Matoba, A. (1985) Corneal allografts induce cytotoxic T cell but not delayed hypersensitivity responses in mice. Invest Ophthalmol Vis Sci 26, 1516-1523, PubMed ID: 86032833
41 Matoba, A.Y, Peeler, J.S. and Niederkorn, J.Y. (1986) T cell subsets in the immune rejection of murine heterotopic corneal allografts. Invest Ophthalmol Vis Sci 27, 1244-1254, PubMed ID: 86277258
42 Callanan, D, Peeler, J. and Niederkorn, J.Y. (1988) Characteristics of rejection of orthotopic corneal allografts in the rat. Transplantation 45, 437-443, PubMed ID: 88146260
43 Minamoto, A. et al. (1994) Induction of cytotoxic T lymphocytes from splenocytes after orthotopic penetrating keratoplasty in the rat. Ophthalmologica 208, 105-109, PubMed ID: 94239703
44 He, Y.G., Mellon, J. and Niederkorn, J.Y. (1996) The effect of oral immunization on corneal allograft survival. Transplantation 61, 920-926, PubMed ID: 96185315
45 Van der Veen, G. et al. (1998) Cytotoxic T lymphocytes and antibodies after orthotropic penetrating keratoplasty in rats treated with dichloromethylene diphosphonate encapsulated liposomes. Curr Eye Res 17, 1018-1026, PubMed ID: 99002354
46 Irschick, E. et al. (1989) Studies of the mechanism of tolerance induced by short-term immunosuppression with cyclosporine in high-risk corneal allograft recipients. I. Analysis of CTL precursor frequencies. Transplantation 48, 986-990, PubMed ID: 90085354
47 Roelen, D.L. et al. (1995) The presence of activated donor HLA class I-reactive T lymphocytes is associated with rejection of corneal grafts. Transplantation 59, 1039-1042, PubMed ID: 95224776
48 Ksander, B.R., Sano, Y. and Streilein, J.W. (1996) Role of donor-specific cytotoxic T cells in rejection of corneal allografts in normal and high-risk eyes. Transpl Immunol 4, 49-52, PubMed ID: 96358151
49 Sano, Y., Streilein, J.W. and Ksander, B.R. (1999) Detection of minor alloantigen-specific cytotoxic T cells after rejection of murine orthotopic corneal allografts: evidence that graft antigens are recognized exclusively via the "indirect pathway". Transplantation 68, 963-970, PubMed ID: 20000335
50 Sano, Y., Ksander, B.R. and Streilein, J.W. (1995) Fate of orthotopic corneal allografts in eyes that cannot support anterior chamber-associated immune deviation induction. Invest Ophthalmol Vis Sci 36, 2176-2185
51 Sano, Y., Ksander, B.R. and Streilein, J.W. (1997) Murine orthotopic corneal transplantation in high-risk eyes. Rejection is dictated primarily by weak rather than strong alloantigens. Invest Ophthalmol Vis Sci 38, 1130-1138, PubMed ID: 97296763
52 Streilein, J.W. (1999) Immunobiology and immunopathology of corneal transplantation. Chem Immunol 73, 186-206, PubMed ID: 20058085
53 Dana, M.R. and Streilein, J.W. (1996) Loss and restoration of immune privilege in eyes with corneal neovascularization. Invest Ophthalmol Vis Sci 37, 2485-2494, PubMed ID: 97087826
54 Dana, M.R., Yamada, J. and Streilein, J.W. (1997) Topical interleukin 1 receptor antagonist promotes corneal transplant survival. Transplantation 63, 1501-1507, PubMed ID: 97318880
55 Dana, M.R. et al. (1998) Interleukin-1 receptor antagonist suppresses Langerhans cell activity and promotes ocular immune privilege. Invest Ophthalmol Vis Sci 39, 70-77, PubMed ID: 98090412

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

56 Streilein, J.W. (1987) Immune regulation and the eye: a dangerous compromise. Faseb J 1, 199-208, PubMed ID: 87305322
57 Streilein, J.W. (1999) Immunoregulatory mechanisms of the eye. Prog Retin Eye Res 18, 357-370, PubMed ID: 99206735
58 Reece-Smith, H. et al. (1981) Prolonged survival of pancreatic islet allografts transplanted beneath the renal capsule. Transplantation 31, 305-306, PubMed ID: 81178183
59 Foglia, R.P. et al. (1986) Fetal allograft survival in immunocompetent recipients is age dependent and organ specific. Ann Surg 204, 402-410, PubMed ID: 87024774
60 McCune, J.M. et al. (1988) The SCID-hu mouse: murine model for the analysis of human hematolymphoid differentiation and function. Science 241, 1632-1639, PubMed ID: 88336897
61 Hori, J., Joyce, N.C. and Streilein, J.W. (2000) Immune privilege and immunogenicity reside among different layers of the mouse cornea. Invest Ophthalmol Vis Sci 41, 3032-3042, PubMed ID: 20424959
62 Tuberville, A.W., Foster, C.S. and Wood, T.O. (1983) The effect of donor cornea epithelium removal on the incidence of allograft rejection reactions. Ophthalmology 90, 1351-1356, PubMed ID: 84118305
63 Stulting, R.D. et al. (1988) Effect of donor epithelium on corneal transplant survival. Ophthalmology 95, 803-812, PubMed ID: 89097897
64 Treseler, P.A., Foulks, G.N. and Sanfilippo, F. (1984) The expression of HLA antigens by cells in the human cornea. Am J Ophthalmol 98, 763-772, PubMed ID: 85069678
65 Whitsett, C.F. and Stulting, R.D. (1984) The distribution of HLA antigens on human corneal tissue. Invest Ophthalmol Vis Sci 25, 519-524, PubMed ID: 84184971
66 Pepose, J.S. et al. (1985) Detection of HLA class I and II antigens in rejected human corneal allografts. Ophthalmology 92, 1480-1484, PubMed ID: 86093180
67 Dreizen, N.G., Whitsett, C.F. and Stulting, R.D. (1988) Modulation of HLA antigen expression on corneal epithelial and stromal cells. Invest Ophthalmol Vis Sci 29, 933-939, PubMed ID: 88227277
68 Sanfilippo, F. et al. (1986) Reduced graft rejection with good HLA-A and B matching in high-risk corneal transplantation. N Engl J Med 315, 29-35, PubMed ID: 86230763
69 Boisjoly, H.M. et al. (1989) Rejection following corneal transplantation. Effect of HLA compatibility of the grafts. Clin Invest Med 12, 221-223, PubMed ID: 92379921
70 Vail, A. et al. (1997) Conclusions of the corneal transplant follow up study. Collaborating Surgeons. Br J Ophthalmol 81, 631-636, PubMed ID: 98009860
71 Volker-Dieben, H.J. et al. (2000) Beneficial effect of HLA-DR matching on the survival of corneal allografts. Transplantation 70, 640-648, PubMed ID: 20426039
72 Beekhuis, W.H. et al. (1991) Corneal graft survival in HLA-A- and HLA-B-matched transplantations in high-risk cases with retrospective review of HLA-DR compatibility. Cornea 10, 9-12, PubMed ID: 91208970
73 The Collaborative Corneal Transplantation Studies Research Group (1992) The collaborative corneal transplantation studies (CCTS). Effectiveness of histocompatibility matching in high-risk corneal transplantation. Arch Ophthalmol 110, 1392-1403, PubMed ID: 93038207
74 Hill, J.C. and Creemers, P.C. (1997) An adverse matching effect for the HLA-B locus in corneal transplantation. Transpl Int 10, 145-149, PubMed ID: 97245243
75 Nicholls, S.M., Bradley, B.A. and Easty, D.L. (1995) Non-MHC antigens and their relative resistance to immunosuppression after corneal transplantation. Eye 9, 208-214, PubMed ID: 96014786
76 Sonoda, Y. and Streilein, J.W. (1992) Orthotopic corneal transplantation in mice—evidence that the immunogenetic rules of rejection do not apply. Transplantation 54, 694-704, PubMed ID: 93032211
77 Gillette, T.E., Chandler, J.W. and Greiner, J.V. (1982) Langerhans cells of the ocular surface. Ophthalmology 89, 700-711, PubMed ID: 83013879
78 Jager, M.J., Gregerson, D.S. and Streilein, J.W. (1995) Regulators of immunological responses in the cornea and the anterior chamber of the eye. Eye 9, 241-246, PubMed ID: 96014792
79 Williamson, J.S., DiMarco, S. and Streilein, J.W. (1987) Immunobiology of Langerhans cells on the ocular surface. I. Langerhans cells within the central cornea interfere with induction of anterior chamber associated immune deviation. Invest Ophthalmol Vis Sci 28, 1527-1532, PubMed ID: 87307210

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

80 McLeish, W. et al. (1989) Immunobiology of Langerhans cells on the ocular surface. II. Role of central corneal Langerhans cells in stromal keratitis following experimental HSV-1 infection in mice. Reg Immunol 2, 236-243, PubMed ID: 90373705
81 Ross, J. et al. (1991) The differential effects of donor versus host Langerhans cells in the rejection of MHC-matched corneal allografts. Transplantation 52, 857-861, PubMed ID: 92055962
82 He, Y.G. and Niederkorn, J.Y. (1996) Depletion of donor-derived Langerhans cells promotes corneal allograft survival. Cornea 15, 82-89, PubMed ID: 97063519
83 Niederkorn, J.Y. (1995) Effect of cytokine-induced migration of Langerhans cells on corneal allograft survival. Eye 9, 215-218, PubMed ID: 96014787
84 Lechler, R.I. and Batchelor, J.R. (1982) Restoration of immunogenicity to passenger cell-depleted kidney allografts by the addition of donor strain dendritic cells. J Exp Med 155, 31-41, PubMed ID: 82099946
85 Hutchinson, I.V. (1994) The immune response to transplanted tissues: recognition and regulation. J Pathol (Suppl.) 173, 238
86 Lafferty, K.J. et al. (1983) Immunobiology of tissue transplantation: a return to the passenger leukocyte concept. Annu Rev Immunol 1, 143-173, PubMed ID: 86050965
87 Jager, M.J. (1992) Corneal Langerhans cells and ocular immunology. Reg Immunol 4, 186-195, PubMed ID: 93264169
88 Gebhardt, B.M. (1990) The role of class II antigen-expressing cells in corneal allograft immunity. Invest Ophthalmol Vis Sci 31, 2254-2260, PubMed ID: 91055925
89 Shoskes, D.A. and Wood, K.J. (1994) Indirect presentation of MHC antigens in transplantation. Immunol Today 15, 32-38, PubMed ID: 94183394
90 Bradley, J.A., Mowat, A.M. and Bolton, E.M. (1992) Processed MHC class I alloantigen as the stimulus for CD4+ T-cell dependent antibody-mediated graft rejection. Immunol Today 13, 434-438, PubMed ID: 93119429
91 Benichou, G. et al. (1992) Donor major histocompatibility complex (MHC) peptides are presented by recipient MHC molecules during graft rejection. J Exp Med 175, 305-308, PubMed ID: 1730925
92 Yamada, J., Streilein, J.W. and Dana, M.R. (1999) Role of tumor necrosis factor receptors TNFR-I (P55) and TNFR-II (P75) in corneal transplantation. Transplantation 68, 944-949, PubMed ID: 20000332
93 Yamada, J. et al. (1998) Interleukin 1 receptor antagonist suppresses allosensitization in corneal transplantation. Arch Ophthalmol 116, 1351-1357, PubMed ID: 99005296
94 Donnelly, J.J. et al. (1985) Induction of class II (Ia) alloantigen expression on corneal endothelium in vivo and in vitro. Invest Ophthalmol Vis Sci 26, 575-580, PubMed ID: 85156833
95 Zhu, S.N. and Dana, M.R. (1999) Expression of cell adhesion molecules on limbal and neovascular endothelium in corneal inflammatory neovascularization. Invest Ophthalmol Vis Sci 40, 1427-1434, PubMed ID: 99285857
96 Luster, A.D. (1998) Chemokines—chemotactic cytokines that mediate inflammation. N Engl J Med 338, 436-445, PubMed ID: 98117072
97 Sallusto, F., Lanzavecchia, A. and Mackay, C.R. (1998) Chemokines and chemokine receptors in T-cell priming and Th1/Th2- mediated responses. Immunol Today 19, 568-574, PubMed ID: 99082467
98 Tang, H.L. and Cyster, J.G. (1999) Chemokine Up-regulation and activated T cell attraction by maturing dendritic cells. Science 284, 819-822, PubMed ID: 99238817
99 Annunziato, F. et al. (1999) Chemokine receptors and other surface molecules preferentially associated with human Th1 or Th2 cells. Microbes Infect 1, 103-106, PubMed ID: 20303683
100 Bonecchi, R. et al. (1998) Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. J Exp Med 187, 129-134, PubMed ID: 98080604
101 Colantonio, L. et al. (1999) Upregulation of integrin alpha6/beta1 and chemokine receptor CCR1 by interleukin-12 promotes the migration of human type 1 helper T cells. Blood 94, 2981-2989, PubMed ID: 20028277
102 Qin, S. et al. (1998) The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. J Clin Invest 101, 746-754, PubMed ID: 98133948
103 Gottlieb, A.B. et al. (1988) Detection of a gamma interferon-induced protein IP-10 in psoriatic plaques. J Exp Med 168, 941-948, PubMed ID:

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

89010519
104 Grandaliano, G. et al. (1997) Monocyte chemotactic peptide-1 expression and monocyte infiltration in acute renal transplant rejection. Transplantation 63, 414-420, PubMed ID: 97192114
105 Pattison, J. et al. (1994) RANTES chemokine expression in cell-mediated transplant rejection of the kidney. Lancet 343, 209-211, PubMed ID: 94118652
106 Fairchild, R.L. et al. (1997) Expression of chemokine genes during rejection and long-term acceptance of cardiac allografts. Transplantation 63, 1807-1812, PubMed ID: 97354215
107 Yamagami, S. et al. (1999) Differential chemokine gene expression in corneal transplant rejection. Invest Ophthalmol Vis Sci 40, 2892-2897, PubMed ID: 20015842
108 Raizman, M. (1996) Corticosteroid therapy of eye disease. Fifty years later. Arch Ophthalmol 114, 1000-1001, PubMed ID: 96326201
109 Poon, A.C. et al. (1999) Systemic cyclosporin A for penetrating keratoplasty: case control study. Invest Ophthalmol Vis Sci 40, S252
110 Barraquer, J. (1985) Immunosuppressive agents in penetrating keratoplasty. Am J Ophthalmol 100, 61-64, PubMed ID: 85248733
111 Rehany, U. and Waisman, M. (1994) Suppression of corneal allograft rejection by systemic cyclosporine-A in heavily vascularized rabbit corneas following alkali burns. Cornea 13, 447-453, PubMed ID: 95087387
112 Mills, R.A. et al. (1995) Topical FK-506 prevents experimental corneal allograft rejection. Cornea 14, 157-160, PubMed ID: 95262422
113 Niederkorn, J.Y, Peeler, J.S. and Mellon, J. (1989) Phagocytosis of particulate antigens by corneal epithelial cells stimulates interleukin-1 secretion and migration of Langerhans cells into the central cornea. Reg Immunol 2, 83-90, PubMed ID: 90373698
114 Staats, H.F. and Lausch, R.N. (1993) Cytokine expression in vivo during murine herpetic stromal keratitis. Effect of protective antibody therapy. J Immunol 151, 277-283, PubMed ID: 93315844
115 Le, J. and Vilcek, J. (1987) Tumor necrosis factor and interleukin 1: cytokines with multiple overlapping biological activities. Lab Invest 56, 234-248, PubMed ID: 87142728
116 Dinarello, C.A. and Wolff, S.M. (1993) The role of interleukin-1 in disease. N Engl J Med 328, 106-113, PubMed ID: 93101156
117 Dana, M.R., Zhu, S.N. and Yamada, J. (1998) Topical modulation of interleukin-1 activity in corneal neovascularization. Cornea 17, 403-409, PubMed ID: 98339567
118 Eisenberg, S.P. et al. (1990) Primary structure and functional expression from complementary DNA of a human interleukin-1 receptor antagonist. Nature 343, 341-346, PubMed ID: 90136921
119 Hannum, C.H. et al. (1990) Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. Nature 343, 336-340, PubMed ID: 90136920
120 Granowitz, E.V. et al. (1991) Interleukin-1 receptor antagonist competitively inhibits the binding of interleukin-1 to the type II interleukin-1 receptor. J Biol Chem 266, 14147-14150, PubMed ID: 91317752
121 Van Klink, F. et al. (1997) Systemic immune response to Acanthamoeba keratitis in the Chinese hamster. Ocul Immunol Inflamm 5, 235-244, PubMed ID: 98116918
122 Dekaris, I., Zhu, S.N. and Dana, M.R. (1999) TNF-alpha regulates corneal Langerhans cell migration. J Immunol 162, 4235-4239, PubMed ID: 99218450
123 Eigler, A. et al. (1997) Taming TNF: strategies to restrain this proinflammatory cytokine. Immunol Today 18, 487-492, PubMed ID: 98019990
124 Sekine-Okano, M. et al. (1996) Expression and release of tumor necrosis factor-alpha by explants of mouse cornea. Invest Ophthalmol Vis Sci 37, 1302-1310, PubMed ID: 96245205
125 Peschon, J.J. et al. (1998) TNF receptor-deficient mice reveal divergent roles for p55 and p75 in several models of inflammation. J Immunol 160, 943-952, PubMed ID: 98211659
126 Kondo, S. and Sauder, D.N. (1997) Tumor necrosis factor (TNF) receptor type 1 (p55) is a main mediator for TNF-alpha-induced skin inflammation. Eur J Immunol 27, 1713-1718, PubMed ID: 97390725
127 Bazzoni, F. and Beutler, B. (1996) The tumor necrosis factor ligand and receptor families. N Engl J Med 334, 1717-1725, PubMed ID: 96240534
128 McComb, J. et al. (1999) Antiarthritic activity of soluble tumor necrosis factor receptor type I forms in adjuvant arthritis: correlation of plasma levels with efficacy. J Rheumatol 26, 1347-1351, PubMed ID: 99308761
129 Zhu, S. et al. (1999) Early expression of

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

proinflammatory cytokines interleukin-1 and tumor necrosis factor-alpha after corneal transplantation. J Interferon Cytokine Res 19, 661-669, PubMed ID: 99360750
130 Qian, Y. et al. (2000) Topical soluble tumor necrosis factor receptor type I suppresses ocular chemokine gene expression and rejection of allogeneic corneal transplants. Arch Ophthalmol 118, 1666-1671, PubMed ID: 20567138
131 Chambers, C.A. and Allison, J.P. (1999) Costimulatory regulation of T cell function. Curr Opin Cell Biol 11, 203-210, PubMed ID: 99227314
132 Linsley, P.S. et al. (1991) CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med 174, 561-569, PubMed ID: 91341416
133 Hoffmann, F. et al. (1997) Inhibition of corneal allograft reaction by CTLA4-Ig. Graefes Arch Clin Exp Ophthalmol 235, 535-540, PubMed ID: 97431126
134 Gebhardt, B.M. et al. (1999) Protection of corneal allografts by CTLA4-Ig. Cornea 18, 314-320, PubMed ID: 99267077
135 Konig Merediz, S.A. et al. (2000) Ballistic transfer of minimalistic immunologically defined expression constructs for IL4 and CTLA4 into the corneal epithelium in mice after orthotopic corneal allograft transplantation. Graefes Arch Clin Exp Ophthalmol 238, 701-707, PubMed ID: 20464262
136 Grewal, I.S. and Flavell, R.A. (1996) The role of CD40 ligand in costimulation and T-cell activation. Immunol Rev 153, 85-106, PubMed ID: 97163973
137 Kirk, A.D. et al. (1999) Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates. Nat Med 5, 686-693, PubMed ID: 99297918
138 Larsen, C.P. et al. (1996) Long-term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways. Nature 381, 434-438, PubMed ID: 96217915
139 Kenyon, N.S. et al. (1999) Long-term survival and function of intrahepatic islet allografts in rhesus monkeys treated with humanized anti-CD154. Proc Natl Acad Sci U S A 96, 8132-8137, PubMed ID: 99324201
140 Paul, W.E. and Seder, R.A. (1994) Lymphocyte responses and cytokines. Cell 76, 241-251, PubMed ID: 94123332
141 Yamada, J. et al. (1999) Mice with Th2-biased immune systems accept orthotopic corneal allografts placed in "high risk" eyes. J Immunol 162, 5247-5255, PubMed ID: 99244889
142 Whitcup, S.M. et al. (1993) Expression of cell adhesion molecules in corneal graft failure. Cornea 12, 475-480, PubMed ID: 94085085
143 Philipp, W. (1994) Leukocyte adhesion molecules in rejected corneal allografts. Graefes Arch Clin Exp Ophthalmol 232, 87-95, PubMed ID: 94208742
144 Larkin, D.F., Calder, V.L. and Lightman, S.L. (1997) Identification and characterization of cells infiltrating the graft and aqueous humour in rat corneal allograft rejection. Clin Exp Immunol 107, 381-391, PubMed ID: 97182740
145 He, Y. et al. (1994) Effect of LFA-1 and ICAM-1 antibody treatment on murine corneal allograft survival. Invest Ophthalmol Vis Sci 35, 3218-3225, PubMed ID: 94321132
146 Yamagami, S. et al. (1995) Suppression of corneal allograft rejection after penetrating keratoplasty by antibodies to ICAM-1 and LFA-1 in mice. Transplant Proc 27, 1899-1900, PubMed ID: 95242561
147 Zhu, S.N. et al. (2000) ICAM-1 deficiency suppresses host allosensitization and rejection of MHC-disparate corneal transplants. Transplantation 69, 1008-1013, PubMed ID: 20216345
148 Hori, J. et al. (1997) Specific immunosuppression of corneal allograft rejection by combination of anti-VLA-4 and anti-LFA-1 monoclonal antibodies in mice. Exp Eye Res 65, 89-98, PubMed ID: 97383206
149 Yamagami, S., Isobe, M. and Tsuru, T. (2000) Characterization of cytokine profiles in corneal allograft with anti- adhesion therapy. Transplantation 69, 1655-1659, PubMed ID: 20294366
150 Klintworth, G.K. and Burger, P.C. (1983) Neovascularization of the cornea: current concepts of its pathogenesis. Int Ophthalmol Clin 23, 27-39, PubMed ID: 83134630
151 Epstein, R.J. and Stulting, R.D. (1987) Corneal neovascularization induced by stimulated lymphocytes in inbred mice. Invest Ophthalmol Vis Sci 28, 1505-1513, PubMed ID: 87307207
152 Dana, M.R. et al. (1995) Corneal neovascularization after penetrating keratoplasty. Cornea 14, 604-609, PubMed ID: 96155580
153 Aiello, L.P. (1997) Vascular endothelial growth factor and the eye: biochemical mechanisms of action and implications for novel therapies.

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994

Ophthalmic Res 29, 354-362, PubMed ID: 97465013
154 Yatoh, S. et al. (1998) Effect of a topically applied neutralizing antibody against vascular endothelial growth factor on corneal allograft rejection of rat. Transplantation 66, 1519-1524, PubMed ID: 99084439
155 She, S.C., Steahly, L.P. and Moticka, E.J. (1990) Intracameral injection of allogeneic lymphocytes enhances corneal graft survival. Invest Ophthalmol Vis Sci 31, 1950-1956, PubMed ID: 91008154
156 Niederkorn, J.Y. and Mellon, J. (1996) Anterior chamber-associated immune deviation promotes corneal allograft survival. Invest Ophthalmol Vis Sci 37, 2700-2707, PubMed ID: 97132028
157 Sano, Y., Okamoto, S. and Streilein, J.W. (1997) Induction of donor-specific ACAID can prolong orthotopic corneal allograft survival in "high-risk" eyes. Curr Eye Res 16, 1171-1174, PubMed ID: 98057520
158 Yamada, J. and Streilein, J.W. (1997) Induction of anterior chamber-associated immune deviation by corneal allografts placed in the anterior chamber. Invest Ophthalmol Vis Sci 38, 2833-2843, PubMed ID: 98079960
159 Sonoda, A. et al. (2000) ACAID induced by allogeneic corneal tissue promotes subsequent survival of orthotopic corneal grafts. Invest Ophthalmol Vis Sci 41, 790-798, PubMed ID: 20174837
160 Strobel, S. and Mowat, A.M. (1998) Immune responses to dietary antigens: oral tolerance. Immunol Today 19, 173-181, PubMed ID: 98237951
161 Garside, P. and Mowat, A.M. (1997) Mechanisms of oral tolerance. Crit Rev Immunol 17, 119-137, PubMed ID: 97248221
162 Weiner, H.L. (1997) Oral tolerance: immune mechanisms and treatment of autoimmune diseases. Immunol Today 18, 335-343, PubMed ID: 97381558
163 Ma, D., Mellon, J. and Niederkorn, J.Y. (1997) Oral immunisation as a strategy for enhancing corneal allograft survival. Br J Ophthalmol 81, 778-784, PubMed ID: 98084912
164 Ma, D., Mellon, J. and Niederkorn, J.Y. (1998) Conditions affecting enhanced corneal allograft survival by oral immunization. Invest Ophthalmol Vis Sci 39, 1835-1846, PubMed ID: 98394389
165 Ma, D. et al. (1998) Immunologic phenotype of hosts orally immunized with corneal alloantigens. Invest Ophthalmol Vis Sci 39, 744-753, PubMed ID: 98199707
166 Auchincloss, H., Jr. (1988) Xenogeneic transplantation. A review. Transplantation 46, 1-20, PubMed ID: 88278422
167 Caplan, A.L. (1992) Is xenografting morally wrong? Transplant Proc 24, 722-727, PubMed ID: 92230025
168 Najarian, J.S. (1992) Overview of in vivo xenotransplantation studies: prospects for the future. Transplant Proc 24, 733-738, PubMed ID: 92230027
169 Platt, J.L. (1996) Xenotransplantation: recent progress and current perspectives. Curr Opin Immunol 8, 721-728, PubMed ID: 97058070
170 Auchincloss, H., Jr and Sachs, D.H. (1998) Xenogenic transplantation. Annu Rev Immunol 16, 433-470, PubMed ID: 98259425
171 Coster, D.J. and Williams, K.A. (1992) Donor cornea procurement: some special problems in Asia. Asia-Pacific Ophthalmol 4, 7
172 Tanaka, K. et al. (2000) Immunobiology of xenogeneic cornea grafts in mouse eyes. I. Fate of xenogeneic cornea tissue grafts implanted in anterior chamber of mouse eyes. Transplantation 69, 610-616, PubMed ID: 20170392
173 Tanaka, K. and Streilein, J.W. (2000) Immunobiology of xenogeneic cornea grafts in mouse eyes. II. Immunogenicity of xenogeneic cornea tissue grafts implanted in anterior chamber of mouse eyes. Transplantation 69, 616-623, PubMed ID: 20170393
174 Ross, J.R., Howell, D.N. and Sanfilippo, F.P. (1993) Characteristics of corneal xenograft rejection in a discordant species combination. Invest Ophthalmol Vis Sci 34, 2469-2476, PubMed ID: 93315304
175 Larkin, D.F. et al. (1995) Experimental orthotopic corneal xenotransplantation in the rat. Mechanisms of graft rejection. Transplantation 60, 491-497, PubMed ID: 95406947
176 Larkin, D.F. and Williams, K.A. (1995) The host response in experimental corneal xenotransplantation. Eye 9, 254-260, PubMed ID: 96014794
177 Tanaka, K., Yamada, J. and Streilein, J.W. (2000) Xenoreactive CD4+ T cells and acute rejection of orthotopic guinea pig corneas in mice. Invest Ophthalmol Vis Sci 41, 827-832
178 Yamagami, S. et al. (2001) Role of CC chemokines and chemokine receptors in corneal Langerhans cell migration (ARVO Abstract). Invest Ophthalmol Vis Sci 42, S575

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994 ©2001 Cambridge University Press

Further reading, resources and contacts

The American Academy of Ophthalmology organises ophthalmic education, meetings and advocacy.
http://www.eyenet.org/

The Eye Bank Association of America procures and distributes eyes for corneal tranplantation, and offers education and research programmes.

http://www.restoresight.org/

The Schepens Eye Research Institute website introduces research projects in the authors' laboratory

http://www.eri.harvard.edu/

Features associated with this article

Figures

Figure 1. Diagrammatic section of the eyeball, showing a close-up of the anterior segment (fig001rdb).
Figure 2. Schematic diagram of the 'afferent' and 'efferent' arms of corneal alloimmunity (fig002rdb).
Figure 3. The direct and indirect pathways of allosensitisation (fig003rdb).
Figure 4. Processes that lead to a cell-mediated immune response against a corneal graft (fig004rdb).

Tables

Table 1. Potential strategies for immune modulation to promote corneal transplant survival (tab001rdb).

Citation details for this article

Ying Qian and M. Reza Dana (2001) Molecular mechanisms of immunity in corneal allotransplantation and xenotransplantation. Exp. Rev. Mol. Med. 16 July, http://www-ermm.cbcu.cam.ac.uk/01003246h.htm

Accession information: (01)00324-6a.pdf (short code: txt001rdb); 16 July 2001
ISSN 1462-3994