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Rejection and acceptance of corneal allografts

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Abstract

Purpose of review

Corneal transplantation is successful in the short term, but the long term prognosis has not improved over the past twenty years. Here, we review recent findings that may contribute to improved corneal allograft survival.

Recent findings

A better understanding of the molecular pathways affecting corneal graft survival has led to more targeted approaches to immune modulation. Co-stimulatory molecule blockade, inhibition of chemokine-chemokine receptor interactions, modulation of apoptotic pathways, and reduction of corneal neovascularization and lymphangiogenesis have been shown to prolong corneal graft survival in animal models. Conventional immunosuppressive drugs have been tested in new combinations and formulations with some success. Two randomised prospective clinical trials in clinical penetrating corneal transplantation have been reported, but there remains little evidence on the long-term outcomes of the newer lamellar corneal graft procedures.

Summary

New approaches to reducing the impact of rejection on corneal graft survival have focussed on topical rather than systemic therapies, and on component corneal transplantation. The most successful experimental strategies have been those in which more than one pathway has been targeted: it now seems likely that to improve clinical allograft survival, simultaneous modulation of multiple axes of the rejection process will be necessary.

Keywords

corneal allotransplantation, topical immunosuppression, immunomodulatory molecules, component grafts

Introduction

Corneal transplantation is a commonly-performed procedure. Irreversible rejection is a major cause of clinical corneal allograft failure, accounting for at least 30% of all failures in registry series. At least seven major reviews discussing the mechanisms of corneal graft rejection have been published over the past year [1-7]. Unlike the case with solid organ transplantation, where graft failure may mean patient death, the loss of a corneal graft is not a life-threatening situation, so that aggressive therapy using drugs with potentially harmful systemic side-effects is rarely justified. Topical therapy with glucocorticosteroid eye drops remains the mainstay of clinical therapy to prevent allograft rejection, with systemic immunosuppression being limited to high-risk cases that are often published as case reports.

Recent findings in experimental models of corneal transplantation

Appropriate animal models are essential for assessing the pathophysiology of corneal allograft rejection, whether it be in penetrating keratoplasty or in one of the newer lamellar techniques.

New animal models

A new model of penetrating keratoplasty that closely mimics the clinical and histopathological features seen in humans has been developed in the outbred miniature pig [8]. The model will be useful in the study of clinically-applicable regimens of immunosuppression, but corneal graft rejection has to be induced by inducing neovascularization of the host cornea prior to transplantation. New small-animal models have been developed in the mouse [9] and rabbit [10] to investigate immunological and functional features of corneal endothelial cell transplantation. When human corneal endothelial cells cultivated on the thermoresponsive biomaterial poly(N-isopropylacrylamide) were grafted as

monolayers to rabbit corneas denuded of endothelium, corneal clarity was gradually restored [10].

Chemokines, antigen presentation and neovascularization

Corneal allograft rejection is associated with the expression of pro-inflammatory cytokines and chemokines. The upregulation of chemokine expression in corneas following exposure to lipopolysaccharide (bacterial endotoxin) or resulting from surgical trauma might be expected, but surprisingly, simple storage of murine corneas in corneal storage media such as Optisol or RPMI 1640 medium has also been shown to result in marked upregulation within the cornea of chemokines such as IP-10 (CXCL10), RANTES (CCL5) and MIP-2 (CXCL2) [11]. Human corneas are often stored in eye banks for several weeks prior to transplantation, but this practice may need to be reassessed.

The presence of chemokine receptor CCR7-positive antigen presenting cells (APCs) in inflamed host corneas in proximity to CCL21+ and LYVE-1+ lymphatics and their subsequent migration to ipsilateral draining lymph nodes was recently demonstrated [12]. This migration was inhibited by subconjunctival injection of a blocking antibody to the CCR7 ligand CCL21, suggesting that the CCR7-CCL21 interaction promotes access of antigen-bearing APCs to the lymph node vasculature [12]. Such chemokine blockade might be a promising approach to preventing APC migration, because it appears relatively specific.

The migration of APCs into or out of the cornea may depend to some extent on the development of new capillaries and lymphatics in the normally avascular cornea. Inhibition of corneal lymphangiogenesis by oral administration of two new vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors led to decreased recruitment of APCs into

the murine cornea, as well as improved corneal allograft survival in mice [13]. However, it seems likely that this systemic approach might be associated with significant side-effects in humans. Targeted gene therapy with a specific VEGF inhibitor might be more clinically applicable. Intraocular over-expression of the VEGF receptor sFlk-1 has been shown to inhibit corneal neovascularization caused by cautery in a rat model [14], but its effect on graft survival in corneal allograft transplantation remains to be demonstrated.

Advances in drug treatments and synthetic delivery systems

New strategies for immunosuppressive therapy in corneal transplantation include examination of different regimens of systemic administration of existing drugs, or alternatively topical therapy with established drugs, enhanced by improved formulations allowing continuous drug delivery. Systemic administration of the malononitrilamide immunosuppressant FK778 resulted in a modest prolongation of rat corneal graft survival [15]. Similarly, systemic administration of the mineralocorticoid-receptor binding steroid spironolactone induced a moderate improvement of rat corneal allograft survival in association with upregulation of interleukin 10 (IL10) in the cornea, and decreased corneal neovascularization [16]. Cyclosporin A is used systemically for high-risk human corneal allografts with limited success, and concerns over its side-effects restrict wider use. Systemic cyclosporin is only moderately effective in preventing corneal rejection when given in conjunction with other immunosuppressive drugs in a high-risk pig model [8], but has shown some promise administered in a subconjunctival silicone implant [17]. Newer immunosuppressive agents have also been used topically in an attempt to delay or prevent corneal allograft rejection. Topical therapy with the calcineurin inhibitor pimecrolimus did not prolong corneal graft survival in a rat keratoplasty model [18], but in contrast, modest prolongation of rat corneal

allograft survival was seen with topical everolimus [19], which has been shown to possess good penetrative properties in organ-cultured pig corneas [20].

Gene therapy

Gene therapy to prevent corneal graft rejection has remained a focus for many investigators. Non-viral methods of gene and siRNA transfer to the cornea utilising nanoparticles [21] or synthetic peptides [22] have also become more reliable. The development of cornea-specific promoters which can be used in association with non-viral delivery system via an eye drop is of interest for transgenes that may benefit from expression in corneal epithelium or stroma [23]. Localised corneal epithelial or stromal reporter gene expression was achieved using the cornea-specific promoters pK12 or pKera3.2, respectively, whilst the control cytomegalovirus (CMV)-promoter driven plasmid resulted in indiscriminate epithelial and stromal gene expression. The effectiveness and kinetics of lentiviral-mediated gene transfer to the cornea in a variety of species has been investigated, making comparison amongst species easier [24].

Co-stimulatory pathway blockade

Broad and non-specific blockade of CD4 by the specific organic ligand J2, administered orally, abrogated T cell activation and improved corneal allograft survival in a high-risk murine model [25]. This report highlights the importance of systemic T cells in the corneal graft rejection process, but the approach would likely result in significant systemic immunosuppression and is thus unlikely to be applicable in clinical corneal transplantation.

The more targeted inhibition of other potent co-stimulatory signals has shown promise in several experimental models. The B7 family comprises both activating and inhibitory molecules (Figure 1), and has drawn particular interest. Inhibition of different positive co-

stimulatory signals has yielded variable results: neither local nor systemic expression of an ICOS-Ig by means of an adenoviral vector was effective in preventing rat corneal graft rejection [26], but systemic blockade of OX40 ligand significantly prolonged graft survival in the mouse [27]. Of particular interest was a report of a novel molecule that targets both co-stimulatory and apoptosis-related pathways using a single molecule [28]. Incubation of donor corneas *ex vivo* prior to transplantation with a CTLA4-FasL molecule in a murine corneal graft model significantly improved graft survival, with the FasL component inducing apoptosis of infiltrating inflammatory cells. This approach also induced tolerance to subsequent donor-specific skin grafts, at least in those animals in which corneal grafts survived beyond 8 weeks.

Programmed death ligands PD-L1 and PD-L2 are down-regulatory B7 superfamily members. PD-L1 was shown to be constitutively expressed in corneal tissue, and PD-L1 blockade with a specific antibody administered systemically enhanced corneal graft rejection [29]. Corneal transplantation in PD-L1 knock-out recipient mice resulted in accelerated rejection of wild-type donor corneas; a similar effect was seen if PD-L1 knock-out donor corneas were transplanted to wild-type recipients. It is possible that localised PD-L1 over-expression may (in conjunction with other therapies) be useful in promoting corneal graft survival.

Modulation of apoptotic pathways

Rather than inducing apoptosis in infiltrating inflammatory cells, other investigators have attempted to prolong corneal graft survival by inhibiting apoptosis of corneal endothelial cells, since programmed cell death is a major mechanism of endothelial cell loss during rejection. Over-expression of bcl-xL following lentiviral viral gene transfer to donor corneal

endothelium was been shown to improve corneal graft survival significantly in a mouse model [30].

In another study, the inhibition of nitric oxide production in activated macrophages during murine corneal allograft rejection inhibited non-caspase-dependent apoptosis in endothelial cells, resulting in indefinite graft survival in some minor histocompatibility-disparate grafts but not in major histocompatibility complex-mismatched animals. [31]. This result was achieved by intraperitoneal or subconjunctival injection of N,N'-diacetyl-L-cystine dimethylester, an agent which reduces the intracellular glutathione content in APCs and dampens Th1 responses [31]. Inhibition of oxidative stress on endothelial cells by systemic injection of a specific inducible nitric oxide synthase enhanced corneal endothelial cell survival in transplanted rat corneas, but did not reduce the overall incidence of allograft rejection [32].

Cytokines and growth factors

Neither systemic nor local adenoviral vector-mediated expression of viral IL-10 or mammalian p40 interleukin 12 resulted in improved corneal allograft survival in a rat model, despite altered cytokine expression profiles in the recipient corneas indicative of a partial Th2 switch [33,34]. In contrast, adenoviral-vector-mediated over-expression of nerve growth factor (NGF) in rat corneas resulted in prolongation of allograft survival, and increased mRNA expression of the Th2 type cytokines interleukin 4 and IL-10 in the grafted corneas [35]. NGF has previously been shown to modulate the switch to a Th2 type immune response. Systemic NGF expression did not improve corneal allograft survival, but the combination of both systemic CTLA4-Ig and local NGF was effective [35].

Recent findings in clinical corneal transplantation

Corneal transplantation is in era of change. Despite a large number of reports of clinical corneal transplantation, few have provided high-level evidence.

Evidence-based outcome studies

Two randomized prospective clinical trials have been reported over the past year. Nguyen *et al* reported that long-term topical steroid improved graft survival following normal-risk penetrating keratoplasty [36]. Since the use of topical steroids is all but universal after corneal transplantation but the dose schedules vary from surgeon to surgeon, the new evidence for the long-term use of topical corticosteroids after corneal transplantation is valuable and overdue. Another study reported from the Cornea Donor Study Investigator Group set out the results from a prospective controlled clinical trial examining the effect of donor age on corneal graft survival [37]. They concluded that the five-year survival rate of grafts using donors under 65 years was not different from the rate for donors over the age of 65 years.

Ghosh and others reported a retrospective observational study which supported a role for long-term oral rather than topical acyclovir after corneal transplantation for herpetic keratitis [38]. Herpetic recurrences were less frequent and visual acuity after surgery was said to be better in those receiving oral acyclovir, but there was minimal difference in graft survival between the groups.

Component corneal transplantation

There is currently more pressure to change the surgical approach to corneal transplantation than at any time since the procedure was first used a hundred years ago. There has been a strong shift towards “component corneal transplantation” and away from full thickness

(penetrating) keratoplasty. The ambit claim is that replacement of only the abnormal layer of the cornea will reduce complications. The procedures fall into two groups, the first including procedures in which the corneal epithelium and stroma down to Descemet's membrane is transplanted, and the second including procedures in which the host endothelium is replaced with donor endothelium, Descemet's membrane and adjacent stroma. The procedures have been widely adopted, but whilst published reports are generally able to confirm the feasibility of the approaches, they fall short of providing comparative data.

Deep anterior lamellar keratoplasty has been widely adopted as the surgical treatment for a number of conditions including keratoconus. Ardjomand *et al* reported a study comparing the visual outscore after lamellar and penetrating corneal transplantation for keratoconus [39]. In this cohort study, those with penetrating grafts achieved better visual acuity. A case series described by Noble *et al* reported post-operative outcomes that were comparable to those reported for penetrating keratoplasty in the past – but no better [40]. The follow-up was short, 6 to 24 months. The status of the procedure as an alternative to conventional penetrating keratoplasty cannot be ascertained without long-term data. Comparative data concerning endothelial transplantation are also sparse. This evolving procedure is at a stage where case reports have given way to large series [41,42]. Two observations from these series give some cause for concern. Firstly, the visual results may be less than expected. In a large series in which the relationship between post-transplantation corneal thickness and acuity was measured in eyes chosen because they did not have macular disease, the visual acuities reported were not particularly impressive [41]. How they compare with the acuities achieved in patients receiving penetrating grafts remains to be determined. Another matter for concern is the low endothelial cell counts in patients after endothelial transplants [42]. This may compromise the long-term outcomes of these grafts, but again this remains to be determined.

Conclusions

New approaches to reducing the impact of corneal allograft rejection on corneal graft survival have focussed on topical rather than systemic therapies, and on component corneal transplantation. These are sensible strategies to minimise the side-effects of potentially harmful systemic treatments. Drugs and biologics targeting key pathways co-stimulation, apoptosis, neovascularization and lymphangiogenesis have attracted particular interest and have led to improved graft outcome in experimental animals. Developments in gene therapy of the cornea have included improved vector design, including cornea-specific promoters. The most successful strategies to reduce the incidence of experimental corneal graft rejection have been those in which more than one pathway has been targeted: it now seems likely that to improve allograft survival clinically, simultaneous modulation of multiple axes of the complex rejection process will be necessary. Randomised controlled clinical trials in clinical penetrating corneal transplantation are finally being reported, so that some high-level evidence to guide practice is becoming available. There is still a dearth of evidence on the long-term outcomes of the newer component corneal graft procedures.

Acknowledgments and disclosure

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References and recommended reading

- 1 Niederkorn JY. Immune mechanisms of corneal allograft rejection. *Curr Eye Res* 2007; 32:1005-1016.
- 2 Williams KA, Coster DJ. The immunobiology of corneal transplantation. *Transplantation* 2007; 84:806-813.
- 3 Anglade E, Yatscoff R, Foster R, Grau U. Next-generation calcineurin inhibitors for ophthalmic indications. *Expert Opin Investig Drugs* 2007; 16: 1525-1540.
- 4 Panda A, Vanathi M, Kumar A, *et al.* Corneal graft rejection. *Surv Ophthalmol* 2007; 52: 375-396.
- 5 Hori J, Niederkorn JY. Immunogenicity and immune privilege of corneal allografts. *Chem Immunol Allergy* 2007; 92:290-299.
- 6 Chong EM, Dana MR. Graft failure IV. Immunologic mechanisms of corneal transplant rejection. *Int Ophthalmol*. 2008;28:209-222.
- 7 Tabbara KF. Pharmacologic strategies in the prevention and treatment of corneal transplant rejection. *Int Ophthalmol* 2008; 28:223-232.
- 8 Tavandzi U, Procházka R, Usvald D, *et al.* A new model of corneal transplantation in the miniature pig: efficacy of immunosuppressive treatment. *Transplantation* 2007; 83: 1401-1403.
- 9 Hayashi T, Yamagami S, Tanaka K, *et al.* A mouse model of allogeneic corneal endothelial cell transplantation. *Cornea* 2008; 27: 699-705.
- 10 Lai JY, Chen KH, Hsiue GH. Tissue-engineered human corneal endothelial cell sheet transplantation in a rabbit model using functional biomaterials. *Transplantation* 2007; 84: 1222-1232.

11 Pillai RG, Beutelspacher SC, Larkin DF, George AJ. Upregulation of chemokine expression in murine cornea due to mechanical trauma or endotoxin. *Br J Ophthalmol* 2008; 92: 259-264.

* This article provides a warning that *ex vivo* storage and manipulation of corneas can influence the expression of chemokines within those corneas, which can result in earlier graft rejection.

12 Jin Y, Shen L, Chong EM, *et al.* The chemokine receptor CCR7 mediates corneal antigen-presenting cell trafficking. *Mol Vis* 2007; 13: 626-34.

13 Hos D, Bock F, Dietrich T, *et al.* Inflammatory corneal (lymph)angiogenesis is blocked by VEGFR-tyrosine kinase inhibitor ZK 261991, resulting in improved graft survival after corneal transplantation. *Invest Ophthalmol Vis Sci* 2008; 49: 1836-1842.

14 Yu H, Wu J, Li H, *et al.* Inhibition of corneal neovascularization by recombinant adenovirus-mediated sFlk-1 expression. *Biochem Biophys Res Commun* 2007; 361: 946-952.

15 Birnbaum F, Schwartzkopff J, Scholz C, *et al.* The new malononitrilamide immunosuppressant FK778 prolongs corneal allograft survival in the rat keratoplasty model. *Eye* 2007; 21: 1516-1523.

16 Otasevic L, Gong N, Ritter T, *et al.* Effects of spironolactone on corneal allograft survival in the rat. *Ophthalmic Res* 2007; 39: 325-329.

17 Lee SS, Kim H, Wang NS, *et al.* A pharmacokinetic and safety evaluation of an episcleral cyclosporine implant for potential use in high-risk keratoplasty rejection. *Invest Ophthalmol Vis Sci* 2007; 48: 2023-2029.

18 Birnbaum F, Schwartzkopff J, Scholz C, Reinhard T. Topical pimecrolimus does not prolong clear graft survival in a rat keratoplasty model. *Graefes Arch Clin Exp Ophthalmol* 2007; 245: 1717-1721.

- 19 Li XQ, Büch G, Otasevic L, *et al.* Prolongation of corneal allograft survival by topical application of everolimus in experimental keratoplasty. *Ophthalmic Res* 2008; 40: 309-314.
- 20 Baspinar Y, Bertelmann E, Pleyer U, *et al.* Corneal permeation studies of everolimus microemulsion. *J Ocul Pharmacol Ther* 2008; 24: 399-402.
- 21 de la Fuente M, Seijo B, Alonso MJ. Bioadhesive hyaluronan-chitosan nanoparticles can transport genes across the ocular mucosa and transfect ocular tissue. *Gene Ther* 2008; 15: 668-676.
- 22 Johnson LN, Cashman SM, Kumar-Singh R. Cell-penetrating peptide for enhanced delivery of nucleic acids and drugs to ocular tissues including retina and cornea. *Mol Ther* 2008; 16: 107-114.
- 23 Tong YC, Chang SF, Liu CY, *et al.* Eye drop delivery of nano-polymeric micelle formulated genes with cornea-specific promoters. *J Gene Med* 2007; 9: 956-966.
- 24 Parker DG, Kaufmann C, Brereton HM, *et al.* Lentivirus-mediated gene transfer to the rat, ovine and human cornea. *Gene Ther* 2007; 14: 760-767.
- 25 Xiao H, Zhang H, Yu ZY, *et al.* J2 prolongs the corneal allograft survival through inhibition of the CD4+ T cell-mediated response in vivo. *Transpl Immunol* 2007; 18: 130-137.
- 26 Fabian D, Gong N, Vogt K, *et al.* The influence of inducible costimulatory fusion protein (ICOSIg) gene transfer on corneal allograft survival. *Graefes Arch Clin Exp Ophthalmol* 2007; 245: 1515-1521.
- 27 Hattori T, Usui Y, Okunuki Y, *et al.* Blockade of the OX40 ligand prolongs corneal allograft survival. *Eur J Immunol* 2007; 37: 3597-604.
- 28 Shi W, Chen M, Xie L. Prolongation of corneal allograft survival by CTLA4-FasL in a murine model. *Graefes Arch Clin Exp Ophthalmol* 2007; 245: 1691-1697.

* This article demonstrates that immunological tolerance can be achieved in experimental corneal allotransplantation by administration of a bifunctional immunosuppressive molecule.

29 Shen L, Jin Y, Freeman GJ, Sharpe AH, Dana MR. The function of donor versus recipient programmed death-ligand 1 in corneal allograft survival. *J Immunol* 2007; 179: 3672-3679.

* Shows that expression of PD-L1 in either donor or recipient cornea is important for corneal graft survival.

30 Barcia RN, Dana MR, Kazlauskas A. Corneal graft rejection is accompanied by apoptosis of the endothelium and is prevented by gene therapy with bcl-xL. *Am J Transplant* 2007; 7: 2082-2089.

* Shows very significant prolongation of murine corneal graft survival following *ex vivo* transduction of the donor cornea with a lentiviral vector carrying the bcl-xL transgene.

31 Yamada J, Hamuro J, Terai K, Kinoshita S. Major histocompatibility complex semi-matching improves murine corneal allograft survival under oxidative macrophage dominancy. *Transplantation* 2007;84:899-907

32 Bourges JL, Torriglia A, Valamanesh F, *et al.* Nitrosative stress and corneal transplant endothelial cell death during acute graft rejection. *Transplantation* 2007; 84: 415-423.

33 Gong N, Pleyer U, Volk HD, Ritter T. Effects of local and systemic viral interleukin-10 gene transfer on corneal allograft survival. *Gene Ther* 2007; 14: 484-490.

34 Ritter T, Yang J, Dannowski H, *et al.* Effects of interleukin-12p40 gene transfer on rat corneal allograft survival. *Transpl Immunol* 2007; 101-107.

35 Gong N, Pleyer U, Vogt K, *et al.* Local overexpression of nerve growth factor in rat corneal transplants improves allograft survival. *Invest Ophthalmol Vis Sci* 2007; 48: 1043-1052.

36 Nguyen NX, Seitz B, Martus P, *et al.* Long-term topical steroid treatment improves graft survival following normal-risk penetrating keratoplasty. *Am J Ophthalmol* 2007; 144: 318-3189.

* This article describes a randomised prospective clinical trial which demonstrates that long-term, low-dose steroids protect against immunologic graft rejection.

37 Cornea Donor Study Investigator Group, Lass JH, Gal RL, *et al.* Donor age and corneal endothelial cell loss 5 years after successful corneal transplantation. Specular microscopy ancillary study results. *Ophthalmology* 2008; 115: 627-632.

* Describes high-level evidence that corneal donor age up to 75 years does not influence subsequent corneal graft survival.

38 Ghosh S, Jhanji V, Lamoureux E, *et al.* Acyclovir therapy in prevention of recurrent herpetic keratitis following penetrating keratoplasty. *Am J Ophthalmol* 2008; 145: 198-202.

39 Ardjomand N, Hau S, McAlister JC, *et al.* Quality of vision and graft thickness in deep anterior lamellar and penetrating corneal allografts. *Am J Ophthalmol* 2007; 143: 228-235.

40 Noble BA, Agrawal A, Collins C, *et al.* Deep anterior lamellar keratoplasty (DALK): visual outcome and complications for a heterogeneous group of corneal pathologies. *Cornea* 2007; 26: 59-64.

41 Marcon AS, Terry MA, Kara-José N, *et al.* Influence of final corneal thickness in visual acuity after deep lamellar endothelial keratoplasty. *Cornea* 2007; 26: 543-5.

42 Terry MA, Wall JM, Hoar KL, Ousley PJ. A prospective study of endothelial cell loss during the 2 years after deep lamellar endothelial keratoplasty. *Ophthalmology* 2007; 114: 631-9.

Figure legend

Figure 1 Potential sites of intervention in corneal allograft rejection

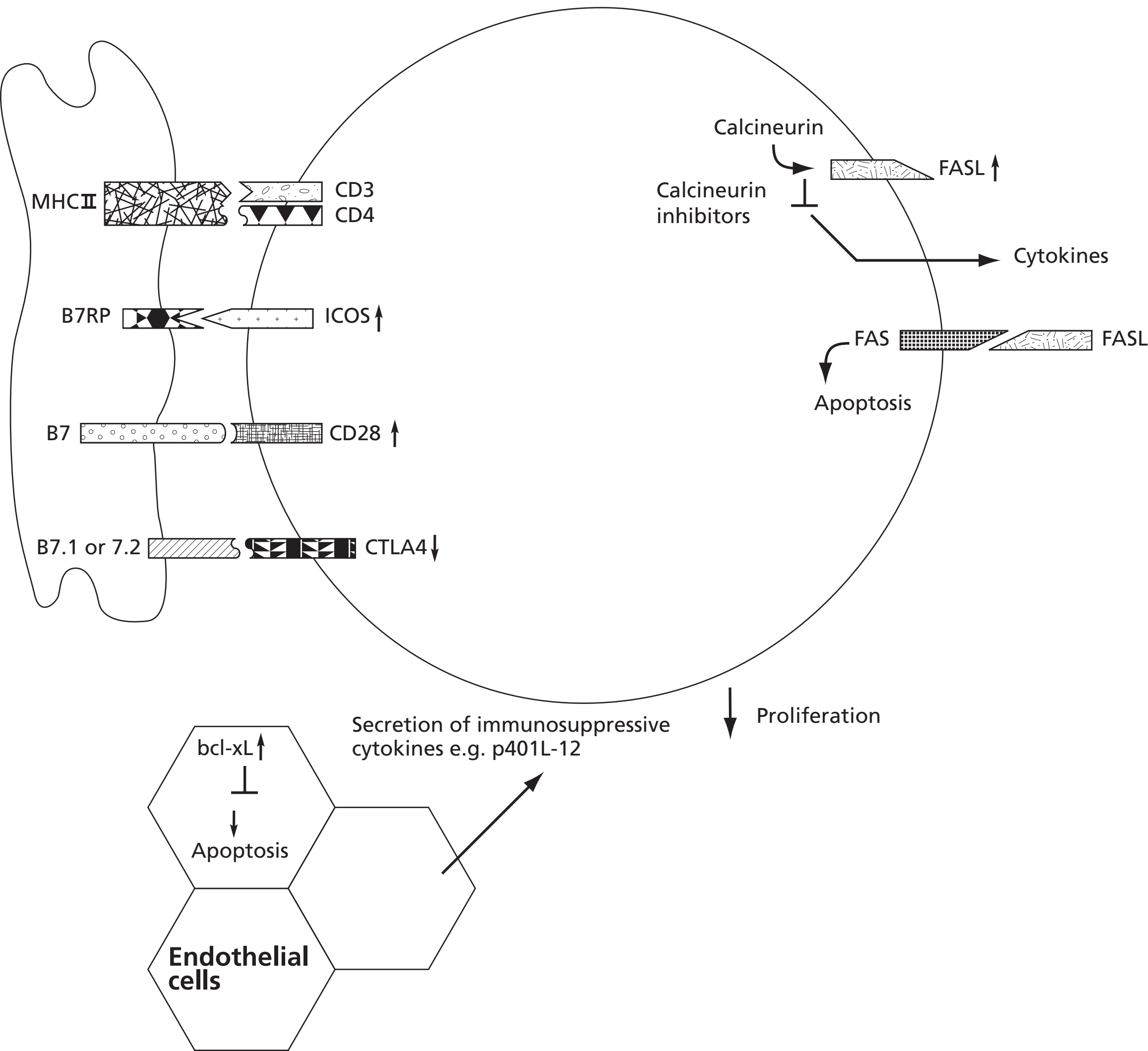
a) Corneal allograft rejection may be prevented by local inhibition or activation of co-stimulatory molecules of the B7 family, depending on their function. Alternatively, inhibition of T cells, by induction of apoptosis in T cells by FasL, calcineurin blockers or immunosuppressive cytokines may be used. Novel therapies have also focused on the corneal endothelium itself, by exposure to molecules that prevent endothelial cell apoptosis in response to damage.

b) Corneal allograft rejection may also be prevented by inhibition of the systemic immune response to a graft. Approaches have included prevention of APC migration to draining lymph node, systemic inhibition of antigen presentation, or use of systemic immunosuppressive drugs.

APC

T Cell

Figure 1. A



APC

T Cell

Figure 1. B

