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Editorial

Monoclonal antibodies in corneal transplantation

Monoclonal antibodies are highly specific and powerful reagents which have proved invaluable in mapping the distribution and dissecting the function of cell-surface antigens, especially on cells of the immune system, and are finding an increasing use in clinical medicine.¹ The murine anti-CD3 monoclonal antibody known as OKT3, with specificity for a cell-surface antigen found on T-lymphocytes, is widely used to reverse corticosteroid-resistant renal allograft rejection episodes and a variety of other antibodies are currently under trial in clinical transplantation studies. Murine monoclonal antibodies directed against human T-cells have already been used as adjuncts to topical corticosteroids in attempts to reverse clinical corneal graft rejection.^{2,3}

As well as having actual or potential uses as immunosuppressive agents in transplantation, monoclonal antibodies can help biologists to understand the underlying mechanisms of graft rejection. One of the more interesting areas of current research concerns the nature of the T-cell that is involved in graft rejection. CD4-positive T-cells, restricted by major histocompatibility complex (MHC) class II antigens, are predominantly involved in helper cell and delayed-type hypersensitivity (DTH) responses, whereas CD8-positive T-cells, restricted by MHC class I antigens, are predominantly involved in cytotoxic cell and suppressor cell responses. The type of T-cell that will accumulate in a rejecting graft is likely to depend to some extent on the type of MHC antigen disparity between donor and host, and both CD4- and CD8-positive T-cells have been observed in rejecting corneal grafts. However, identification of the major subset of T-cells accumulating in mismatched grafts should allow therapy directed against specific effector cells to be targeted more precisely.

In a paper published in this issue of the journal, Ayliffe and colleagues have demonstrated that euthymic rats, chronically depleted of CD4-positive cells by multiple intraperitoneal injections of monoclonal antibody prior to graft, show significant prolongation of orthotopic corneal graft survival when compared with control animals treated with monoclonal antibody of irrelevant specificity. A small number of grafts survived indefinitely in the anti-CD4-treated rats. Depletion of CD8-positive cells, in contrast, had no effect on corneal graft survival in a separate group of animals. The authors suggest that CD8-positive cells are not important in corneal allograft rejection but that CD4-positive cells may play a critical role. In an outbred model of orthotopic corneal transplantation in the rabbit, it has recently been shown that

the cells infiltrating unmodified, rejecting grafts are heterogeneous, but contain a substantial proportion of granulocytes and macrophages indicative, perhaps, of a DTH-like response.⁴

The graft survival data reported by Ayliffe *et al* are similar to those recently obtained in a mouse model of orthotopic corneal transplantation by He *et al*,⁵ in which intraperitoneal injections of monoclonal antibody to CD4 but not to CD8, given on four occasions, were found to prolong orthotopic corneal graft survival across a major MHC mismatch in adult thymectomised mice. Duguid *et al* have shown that an antibody to CD4 will prolong the survival of human corneal xenografts transplanted heterotopically to the subcapsular renal space in the mouse.⁶

Recent experimental studies in a variety of transplantation systems have suggested that a short course of monoclonal antibody therapy, given systemically in the perioperative period, can prolong graft survival and can induce a form of specific transplantation tolerance in some animals.⁷ The most promising studies have involved the use of anti-CD4 antibodies,⁸ though useful results have also been obtained with antibodies to other determinants. The ability to induce specific donor non-responsiveness in the recipient of a corneal graft is a long standing goal of many clinicians. This goal may never be met but it seems possible that the use of monoclonal antibodies may at least provide useful, specific immunosuppressive agents to reduce the incidence of rejection in high risk recipients and to reverse otherwise intractable rejection episodes.

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