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Mechanism of Tolerance Following Class II Gene Transduction of Autologous Swine Bone Marrow

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PREVIOUS findings in miniature swine have demonstrated that matching of major histocompatibility complex (MHC) class II has overwhelming importance in determining the fate of vascularized allografts. In addition, class I mismatched renal allografts are accepted permanently after a course of cyclosporine A (CyA).[1] Therefore, we have used a combination of transduction of class II DRB gene matched to the allograft kidney into autologous bone marrow cells and a short postoperative course of CyA in an attempt to induce tolerance to a fully MHC mismatched kidney transplant (KTx) 6 months later. To date, 3 of 4 class II DRB gene transduction animals have had longer graft survival than control gene transduction animals. We have examined the possible tolerance of the direct and indirect pathways of class II antigen recognition in mixed lymphocyte reaction (MLR) of both a post bone marrow transplant (BMT)/pre KTx animal and a post KTx animal. Furthermore, to assess the possible role of the transduced class II gene in tolerance induction, specific anti-DR and anti-DQ monoclonal antibodies (mAbs) were used to block MLR.

MATERIALS AND METHODS

Fresh PBMC from swine receiving autologous BMT transduced with an allogeneic DRB gene[2] and from naive swine of the same SLA haplotype were used as responders. PBMC from swine bearing the same class II gene as that used for transduction and from a third party haplotype were used as stimulators, respectively. The stimulator cells were irradiated with 25 Gy. Antigen presenting cells (APC) were depleted by flask adhesion and nylon wool columns. Functional assays were used to demonstrate effectiveness of the APC depletion in all assays. Purified anti-class II DR (ISCR3) and DQ (TH16) mAbs were added separately and together to block the MLR.

RESULTS AND DISCUSSION

In an animal showing tolerance to an allogeneic KTx bearing the class II gene used for transduction, hyporesponsiveness to stimulator cells of the donor genotype was observed in MLR. The response that remained was blocked much less completely by anti-DR than by anti-DQ mAbs in the direct pathway of activation, but there was no difference in the indirect pathway. The effect of the transduced class II gene appeared to function mainly in the direct pathway post-KTx. On the other hand, in an animal which had not received a kidney graft, no differences were observed between the responses of DRB gene transduced swine and those of naive swine in assays of direct recognition. However, the tendency of less inhibition by anti-DR mAb was observed in the indirect pathway compared with naive swine. The effect of transduced DRB gene appeared to be observed mainly in the indirect pathway before KTx. Allogeneic class II DRB gene transduction appears to mimic the effect of class II matching with respect to a subsequent allogeneic KTx. The MLR studies prior to and after KTx suggest that even a partial effect of the transduced gene, as observed in vitro, appears to be sufficient to allow tolerance to be induced by the vascularized graft in vivo.

REFERENCES

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