Characterization of Xenograft Resistance to Autoimmune Disease Recurrence After Pancreas Islet Transplantation

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AUTOIMMUNE disease recurrence (ADR) in pancreas islet grafts has been reported to cause a high percentage of all graft losses following islet transplantation in both experimental and clinical islet transplantation. This reaction is a predictable result of the reactivation of a pre-existing autoimmune process. Because autoimmune diseases involve a variety of immune mechanisms, most of which have been poorly characterized, and because immunosuppressive drugs do not block the process, treatment of this destructive process is difficult.

In 1992, our group suggested that islet xenografts were highly resistant to ADR because porcine islets had a strikingly low incidence of ADR when transplanted into NOD mice, whereas allograft islets had a high incidence (70% to 80%) of ADR. Recently, our group transplanted xenograft islets into three primates all of whom are currently off immunosuppressive drugs for (70% to 80%) of ADR. Recently, our group transplanted xenograft islets into three primates all of whom are currently off immunosuppressive drugs for >6 months and without ADR. These results suggest that xenograft islets are highly resistant to ADR and the autoimmune disease state. In this study we attempted to further investigate the phenomenon of xenograft islets resistant to ADR and to focus further on this mechanism by comparing ADR in concordant (CI) and discordant donor islets (DI).

MATERIALS AND METHODS

Three groups of donor islets transplanted to the NOD mice were studied. In group I, donor islets from C3H mice were used; in group II, concordant xenograft (Lewis rat) islets were transplanted; and in group III, discordant islets (pig) were transplanted. NOD mice (n = 60, 20 in each group) were given 500 islets, separated by collagenase digestion in the case of the mice and rat islets, and by a modification of the technique of Ricordi for the pig islets. All islets were cultured for 5 days prior to transplantation under the kidney capsule. All NOD mice had three or more blood sugar (BS) determinations of >300 mg%. All islets functioned initially and rejection or ADR was diagnosed when the BS was >250%. In histopathologic studies of 23 islet implants, we developed criteria for the differentiation of islet rejection (IR) and ADR. In some sections, selective inflammation and islet cell damage in the central (β-cell) region of the islets could be discerned. In other nonfunctional islets, the islet damage was rather homogeneously distributed and peri-islet inflammation was often present. This clinical picture was felt to be more consistent with rejection, although the final diagnosis was made on the basis of antibody stains for glucagon and insulin. The insulin:glucagon stain ratio was >2.0 ± 0.6 in rejection in which some insulin staining cells were often seen.

In contrast, the insulin:glucagon ratios were <1.0 in ADR, indicating a selective destruction of β-cells due to ADR. A two-observer consensus of the diagnosis was obtained in all cases.

All recipients were treated with a 3-day course of rabbit antithymocyte globulin (RATG) and 14 days of deoxyspergualin (DSG). This regimen was found to prolong markedly both allo- and xenoislets in other studies. In the allograft group (n = 20), 15 of 20 grafts were lost to ADR and 4 grafts lost to rejection, with a mean survival of 22 days and a maximum survival of 40 days. In the concordant xenograft (Lewis rat) islet group, 15 grafts were lost to ADR and 5 to rejection with a mean survival time of 28 days and a maximum of 38 days. Neither the difference between the islet survival nor the causes of graft loss were significantly different between these two groups. In contrast, all discordant islet (pig) grafts survived >100 days and there was no graft loss due to ADR or early rejection (P < .05 with the other two groups). Radioimmunoassay (RIA) documented function of pig islets by pig insulin secretion to rule out return of native islet function after STZ treatment. In all discordant islets, pig insulin levels were undetectable at 100 days and in three animals, nephrectomy of the kidney containing the pig islets caused prompt return to the diabetic state.

DISCUSSION

This study was an extension of a previous report by our group demonstrating resistance of xenograft islets to ADR. In this study, we examined whether this resistance was seen with all types of xenograft islets or rather was proportional to the degree of xenograft disparity. Some feel that all xenograft rejection is due to similar mechanisms, involving a humoral predominance and a weak T-cell response and perhaps a reliance on species or minor antigen differences rather than MHC differences. Others have pointed to a predominant cellular response in concordant xenografts with some evidence of greater T-cell participation. These data argue that CX and DX reactivity are quite different, at
least in regard to ADR and perhaps rejection also. Our group has studied immune reactivity to pig islets in a variety of models. We found, in virtually all models tested, that xenograft rejection is often less difficult to control than allograft rejection. In human kidney transplants, Reemstma found allograft and CX rejections to be very similar and about equally difficult to reverse.2 Recently, we noted exceptionally good control of CX rejection and long-term survival in a group of primates with islet xenografts. One animal has been euglycemic for nearly 1 year and two for >6 months. Thus, these animals apparently had no ADR despite the insulinopenic type I diabetic pattern in the six recipients transplanted. The pig islet results reported here suggest that ADR can be avoided with the use of discordant islet xenografts, but not necessarily with CX islets or allografts. The DI donor may be optimal at present.

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REFERENCES