Significant Manipulative Procedures to Reduce Immunogenicity of Human Islet Allografts

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SUCCESSFUL TRANSPLANTATION of pancreatic islets will depend on a better knowledge of those cells which contribute highly to allograft immunogenicity but not to the desired graft function. This knowledge, based upon morphologic and functional in vitro data, appears to be crucial for a successful reduction of graft immunogenicity.

MATERIALS AND METHODS

Immunofluorescence studies and mixed lymphocyte islet culture (MLIC) tests were performed using cryopreserved crude human islet preparations[1] and various HLA- as well as cell type-specific monoclonal antibodies in order to (a) locate the potentially immunogenic cells and (b) demonstrate their functional relevance before and after antibody incubation. Microscopic evaluation of exocrine and endocrine tissue components of crude islet preparations was greatly facilitated by the islet-specific dithizone staining technique.[2]

RESULTS

Immunofluorescence

Using dithizone counterstaining, the vast majority of MHC class II-positive cells was found to be located in the exocrine tissue portion; these cells strongly expressed HLA-DR/DP but very rarely HLA-DQ. By contrast (and in contrast to rodent models), the endocrine tissue portion, ie, pure islets, contained only few and very weakly stained HLA-DR/DP positive cells. Importantly, and in contrast to our experience with rat islets, endocrine beta cells were always HLA-DR/DP/DQ-negative.

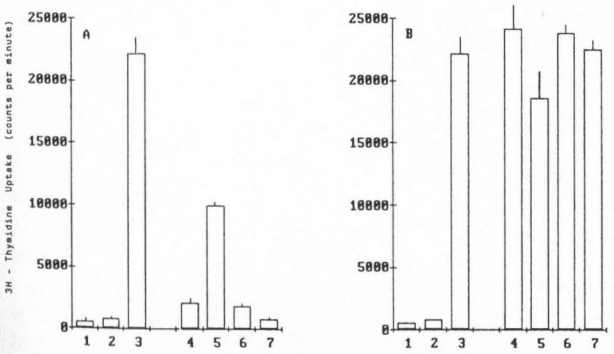

Fig 1. Human mixed lymphocyte islet culture (MLIC): Inhibition by (A) HLA-DR/DP monoclonal antibody and (B) rat MHC class II monoclonal antibody (specificity control). Column (col.) 1, 10^6 responder lymphocytes from peripheral blood + medium; col. 2, 40 HLA-mismatched, mitomycin C-treated stimulator islets + medium; col. 3, uninhibited allogeneic response as control; col. 4-col. 7, allogeneic response after varying treatment protocols: col. 4, pretreatment of responder cells with HLA-DR/DP antibody TÜ39 or rat I-E antibody OX17; col. 5, pretreatment of stimulator islets with TÜ39 or OX17; col. 6, pretreatment of both responder cells and stimulator islets; col. 7, permanent presence of the respective antibody during the 5-day culture period.

Mixed Lymphocyte Islet Culture

Crude islet preparations with 30-40 islets acted as powerful stimulators in MHC-allogeneic MLIC. By contrast, the allogeneic response was markedly reduced when clean, hand-picked stimulator islets were used. This allogeneic response was reduced still more by preincubation of the responder lymphocytes and/or the crude islet preparations with HLA-DR/DP antibodies, as shown in Fig 1.

CONCLUSIONS

(I) According to the morphologic findings, the predominance of MHC class II-positive cells in the exocrine pancreas portion, compared with islets, is expressed much more strongly in the human than in rodents. (II) According to the functional findings, the immunogenicity of these cells can be inhibited by an MHC class II antibody. (III) This functional inhibition appears to be more important the less purified the islets are—that is, the more they are contaminated by exocrine tissue debris.

REFERENCES

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