Long-Term Survival of Donor-Specific Pancreatic Islet Xenografts in Fully Xenogeneic Chimeras (F344 Rat to B10 Mouse)


THE development of procedures to isolate large numbers of purified human pancreatic islet cells has made it possible to initiate a new phase of clinical trials in pancreatic islet transplantation for treatment of type 1 diabetes.1-3 Although nonspecific immunosuppressive agents have been instrumental in controlling alloreactivity to transplanted islet cells, rejection still occurs and is a major limitation to islet transplantation.4 The induction of donor-specific transplantation across a species barrier, using bone marrow stem cells to produce chimerism, has been suggested as a potential approach to prevent rejection of transplanted cells and overcome the shortage of available grafts. We recently reported that acceptance of donor-specific islet cell xenografts was achieved in fully xenogeneic chimeras (WF rat to B10 mouse) when WF rat (Rt1A 0) was the xenogeneic donor. To exclude a strain-specific effect, we have now evaluated whether similar tolerance would be present when F344 rat (Rt1A 1) was used as the xenogeneic donor. We report here that long-term acceptance and function of donor-specific (F344 rat) xenogeneic pancreatic islet grafts could be achieved in fully xenogeneic chimeras (B10 mouse + F344 rat to B10 mouse).

MATERIALS AND METHODS

Fully xenogeneic chimeras were prepared as previously described.5 Chimeras were made diabetic by a single intravenous injection of streptozotocin (165 mg/kg). Rat pancreatic islets were obtained and transplanted as previously reported.6

RESULTS AND DISCUSSION

After placement of either donor-specific F344 rat or third-party WF islet cell xenografts, normoglycemia occurred, indicating technical success. The survival of donor-specific F344 rat pancreatic islet xenografts was significantly prolonged (mean survival time [MST] 180 days; Fig 1). In contrast, major histocompatibility complex-disparate third-party WF rat islets were rapidly rejected, as evi­denced by return of hyperglycemia (MST, 8 days). The donor-specific F344 grafts were functional to maintain the normoglycemic state in chimeras. This study demonstrates that long-term survival and function of donor-specific pancreatic islet xenografts could be obtained in fully xenogeneic chimeras and was not limited to a single strain as the xenogeneic donor.

ACKNOWLEDGMENTS

The authors thank Michelle Waters for manuscript preparation, Richard James and Kathie Karr for technical assistance, and Marissa Mazzucchetti and Mary Oles for animal care.

REFERENCES


From the Pittsburgh Transplant Institute, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania.

Supported in part by the Juvenile Diabetes Foundation, National Institutes of Health Grant No. RO1 AI301 1501A1, the National Institutes of Health Shannon Award, and the American College of Surgeons Fellowship Award (1990–1991).

Address reprint requests to Dr Yijun Zeng, Department of Surgery, University of Chicago, 5847 S Maryland Ave, Box 77, Chicago, IL 60637.

© 1992 by Appleton & Lange
0041-1345/92/$3.00/0