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

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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 ($RtIA^u$) was the xenogeneic donor. To exclude a strain-specific effect, we have now evaluated whether similar tolerance would be present when F344 rat ($RtIA^1$) 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.

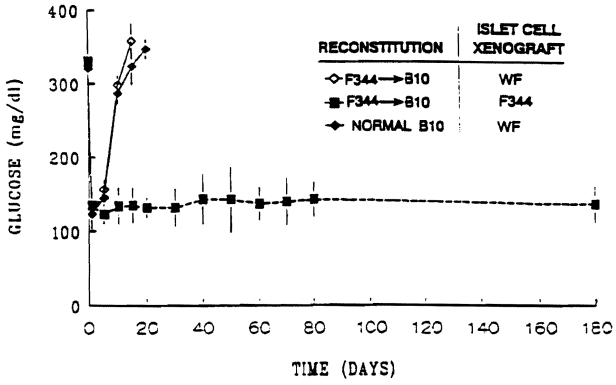

Fig 1. Kinetics of blood glucose determination after streptozotocin, after placement of a donor-specific islet cell xenograft in fully xenogeneic chimera.

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REFERENCES

1. Scharp DW, Lacy PE, Santiago JV, et al: Transplantation 51:76, 1991
2. Tzakis QAG, Ricordi C, Alejandro R, et al: Lancet 18:402, 1990
3. Scharp DW, Lacy PE, Santiago JC, et al: Diabetes 35:515, 1990
4. Kahan B, Van Buren C, Bioleau M: Transplantation 35:9, 1983
5. Ildstad ST, Wren SM, Boggs SS, et al: J Exp Med 8:467, 1991
6. Zeng Y, Ricordi C, Tzakis QAC, et al: Transplantation (in press)

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