1538

Intrapancreatic Islet Transplantation as a Potential Solution to Chronic Failure of Intraportal Islet Grafts

H.L.R. Rilo, P.A. Fontes, A.K. Nussler, A.J. Demetris, P.B. Carroll, S.T. Ildstad, A.G. Tzakis, T.E. Starzl, and C. Ricordi

RECENT progress in islet isolation and purification technology has contributed to the first successful cases of human islet transplantation.[1] The liver was used as the target organ of human islet allografts in most cases. Chronic failure of intraportally transplanted islets has been observed in both large animals and humans, leading investigators to question whether the liver is the ideal site for islet implantation. In a preliminary study, 11 dogs received intraportal islet autografts (13,000 to 16,000 equivalent islets/kg of recipient body weight) following total pancreatectomy.[2] Failure of the islet grafts was observed within 18 months in all animals (in preparation).

Because nitric oxide (NO) toxicity to islets has been recently demonstrated,[3] these results encouraged us to test whether hepatic cells can generate higher levels of NO during 24-hour culture in the presence of a cytokine mixture (interleukin [IL]-1, tumor necrosis factor [TNF]-α, interferon [IFN]-γ) and LPS.

The results indicated that hepatic cells were able to generate significantly higher levels of NO in response to the stimulatory mixture, independently from the presence or absence of islets.[4] In contrast, islets with or without pancreatic exocrine tissue produced significantly lower levels of NO. The observation of chronic failure of intrahepatic islet transplants and the relative inability of the pancreas to generate NO in response to inflammatory cytokines encouraged us to test the pancreas as an alternative site for islet implantation in dogs.

MATERIALS AND METHODS

Seven mongrel dogs received islet autografts following partial pancreatectomy (3/4). The islets were separated by the automated method and purified on Eurocollins–Ficoll gradients using a COBE cell separator.[1] Purified islets (volume < 1 mL) were implanted into the residual pancreatic segment using a 27-gauge needle. Four weeks after autotransplantation, animals were killed for analysis of morphological integrity of the intrapancreatic islet grafts (hematoxylin eosin staining and immunoperoxidase staining for insulin).

RESULTS AND DISCUSSION

Intrapancreatic islet injection was uneventful. Amylase and glucose levels remained within the normal range for the duration of the study. Large aggregates of well-preserved islet cells with a normal degree of β-granulation were present at the sites of intrapancreatic islet infusion. Interestingly, no mononuclear cell infiltrate was present in the area of the implants. These results indicate that the pancreas could be an ideal site for transplantation of highly purified islet preparations. Studies are in progress to determine the functional integrity of intrapancreatic islet grafts and establish whether chronic failure of islet transplants will be prevented in this alternative site.

Chronic failure of intrahepatic islets even in autografts could be explained by continuous exposure to enteric pathogens and endotoxins that reach the liver through the portal circulation. This could result in generation of higher levels of NO. Stimulated NO generation by hepatic cells could also explain why multiple donors have been necessary to normalize glucose levels after human islet transplantation into an allogeneic liver. In this case, the local activation of antigen-presenting cells could generate high levels of NO in the microenvironment at the transplant site.

The authors thank Brenda Smith for technical assistance.

REFERENCES

1. Ricordi C (ed): Pancreatic islet cell transplantation; 1892–1992: One Century of Transplantation for Diabetes. Austin, TX, R.G. Landes, CRC Press, Boca Raton, FL, (distributor), 1992

2. Zeng Y, Ricordi C, Lendoire J, et al: Surgery (in press)

3. Corbett JA, McDaniel ML: Diabetes 41:897, 1992

4. Nussler AK, Carroll PB, DiSilvio M, et al: Transplant Proc (in press)

From the University of Pittsburgh Transplantation Institute, Pittsburgh, Pennsylvania.

Supported in part by the Juvenile Diabetes Foundation, Research Grant 1911421.

Address reprint requests to Dr Camillo Ricordi, Biomedical Science Tower, Terrace & Lothrop Street, Pittsburgh, PA 15213.

0041-1345/93/$3.00/+0