Clinical Islet Xenotransplantation: A Step Forward

Burcin Ekser a,⁎, Rita Bottino b, David K.C. Cooper c

a Transplant Division, Department of Surgery, Indiana University School of Medicine, Indianapolis, IN, USA
b Institute for Cellular Therapeutics, Allegheny-Singer Research Institute, Pittsburgh, PA, USA
c Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA, USA

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With the encouraging results of pancreatic islet allotransplantation, increasing attention is being directed towards pig islet xenotransplantation, which would resolve the problem of islet supply (Markmann et al., 2016; Ekser et al., 2012). Free (nonencapsulated) pig islets (either wild-type or genetically-engineered) have maintained normoglycemia in immunosuppressed diabetic nonhuman primates for > 1 year (Park et al., 2015). Immunoisolated (encapsulated) pig islets have maintained normoglycemia in non-immunosuppressed diabetic nonhuman primates for up to 6 months (Dufrane et al., 2006).

Groth et al. performed the first clinical islet xenotransplantation in 1994 using fetal porcine islet-like cell clusters placed under the kidney capsule (Groth et al., 1994). Although clinical benefit was not demonstrated, evidence was provided by measurement of porcine C-peptide that porcine islets could survive in the human body. The first nationally-regulated clinical trial of intra-peritoneal alginate-poly-L-ornithine-mates for up to 6 months (Dufrane et al., 2006).

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(ii) Encapsulation of pig islets and the immune response
Although the great theoretical advantage of the transplantation of encapsulated islets is that exogenous immunosuppressive therapy may not be required, the long-term viability of the encapsulated islets remains questionable. The dilemma in APA-based encapsulated islets is that, if the islets are not revascularized, they are likely to become exhausted (and die) from lack of nutrients and oxygen, particularly as some fibrin accumulates around the capsules, possibly reducing their permeability. In contrast, if the islets are revascularized, they are likely to become susceptible to injury from an immune or inflammatory response. There is already evidence that APA-based microcapsulated porcine islets induce an inflammatory response, upregulating inflammatory

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⁎ Corresponding author at: Transplant Division, Department of Surgery, Indiana University School of Medicine, 550 University Blvd, Room 4601, Indianapolis, IN 46202, USA.
E-mail address: bekser@iupui.edu (B. Ekser).

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cytokines and activating innate immune cells, such as tumor necrosis factor-α, IL-6, interferon-γ, macrophages, neutrophils, and dendritic cells (Cooper et al., 2016). The great deficiency of the present study is that the authors did not investigate whether there was an immune response to the islets (or capsules), though they speculated that microcapsules might shed xeno-antigens which activate the recruitment of CD4+ T cells and macrophages around the capsule. It will be essential to determine whether there is an immune response to the pig islets. If there is, either modification of the capsules or the administration of exogenous immunosuppressive therapy will be necessary, unless the islets can be completely protected by genetic manipulation of the pig.

Our own opinion is that it will be difficult to totally protect the encapsulated islets from the effects of cytokines and chemokines and possibly other components of the immune response, and therefore some immunosuppressive therapy may prove inevitable, thus negating the major theoretical advantage of ‘immunoisolation’. Nevertheless, as the number of pancreases from deceased humans that become available will never suffice to cure all patients with T1D, the pioneering studies by Matsumoto and his colleagues are important and timely.

Disclosure

The authors declared no conflicts of interest.

References