Achieving and Maintaining Insulin Independence in Human Islet Transplant Recipients

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For islet transplants to complete the transition from clinical research to clinical care, restoration of insulin independence must be achieved—as with pancreas transplants—with a single donor. To achieve this critical milestone more consistently, it will be imperative to pursue the following complementary strategies simultaneously: 1) enhancing the metabolic potency, inflammatory resilience, and immune stealth of isolated islets; 2) inhibiting the thrombotic and inflammatory responses to transplanted islets; and 3) achieving immune protection with strategies lacking diabetogenic side effects. Maintaining insulin independence will be a different challenge requiring us to clarify whether failure of initially successful islet allografts in type 1 diabetes is related: 1) failure of immunosuppressive regimens to control alloimmunity and autoimmune; 2) failure of islet regeneration in the presence of currently applied immunosuppressive regimens; and/or 3) failure of islet neogenesis in the absence of an adequate mass and viability of cotransplanted/engrafted islet precursor cells.

The article by Olle Korsgren et al. in this Forum provides a critical and insightful analysis of issues of particular importance to the field of human islet transplantation. The main message of this thought-provoking review is that the donor: recipient ratio in islet transplantation needs to be reduced to 1:1 and that our efforts to achieve this milestone should focus on minimizing islet loss in the immediate posttransplant period.

Korsgren et al. carefully reevaluated the number of islets present in a human pancreas and concluded that only limited improvements in islet yields obtained from a human donor pancreas can be expected. I assume Korsgren et al. did not intend to suggest that chasing elusive islets is no longer worthwhile and that we should direct all our attention toward peritransplant recipient management for the purpose of maximizing islet engraftment. While it seems fair to assume that the islet yields veteran islet isolators are able to obtain from a pancreas will soon plateau, my prediction is that we are about to witness unprecedented improvements in other, presumably more important qualities of isolated islets such as metabolic potency, inflammatory resilience, and immune stealth. Expanded islet product testing including increasingly sensitive assays of islet potency as well as progressively more defined molecular profiles associated with resistance to inflammatory mediators and the islets’ inflammatory potential will not only enhance the predictive value of islet product release assays but will also at last help define a high-quality islet and thereby guide us in manufacturing superior islets less prone to destruction in the immediate posttransplant period. Minimizing inflammation in brain-dead donors, employing next generation pancreas preservation methods, redefining cytoprotective islet preparation media, exploiting the magnetophoretic mobility of islets loaded with magnetic beads, enhancing islets by delivering cytoprotective peptides by means of protein transduction domains, and modulation of islet surfaces are just some of the real opportunities now available to improve the potency, resilience, and stealth of islets for the purpose of lessening posttransplant islet loss (1–4). I assume Korsgren et al. intended to suggest that islet isolators must raise their standards and strive to become more analytic isletologists and more resourceful islet engineers.

Mitigating thrombotic/inflammatory reactions to transplanted islets has been proposed by Korsgren et al. as the foremost strategy to minimize posttransplant islet loss. Work toward this end may require us to abandon one of our most faithful companions, that is, the portal vein as an islet implantation site. An extravascular site for islet transplant will circumvent the cascade of events elicited when thrombogenic islets are transplanted to an intravascular location, such as the portal vein, where they come immediately in direct contact with blood. A site chosen with some foresight like the omental pouch (5) could meet other criteria of an ideal implantation site such as: 1) easy access to implant and biopsy; 2) lack of exposure to elevated levels of orally administered immunosuppressants; and 3) true portal delivery of insulin and more effective inhibition of hepatic glucose production. Moreover, an alternative site should preferably also allow for prevascularization and implantation of islets alongside with biodegradable scaffolds releasing angiogenic, antiapoptotic, antiinflammatory, and immunoregulatory factors.

For single-donor islet transplants to succeed on a consistent basis it will be imperative to pursue complementary strategies simultaneously. Avoiding the adverse effects of calcineurin inhibitors on islet neovascularization, insulin secretion, and insulin action is expected to increase the success rates of marginal-mass, single-donor islet transplants. At least three corticosteroid- and calcineurin inhibitor-free immunotherapeutic regimens have proven effective in preventing islet allograft rejection in the preclinical nonhuman primate model: 1) anti-CD3 immunotoxin combined with deoxyspergualin (6); 2) basiliximab combined with LEA29Y and sirolimus (7); and 3) basiliximab combined with FTY720 and everolimus (8). The safety and efficacy of all three protocols will...
soon be evaluated in the clinical setting of islet allografts in type 1 diabetic recipients.

There is data to support the optimistic view that single-donor islet allografts will soon match the success rates of islet autografts and vascularized pancreas allografts. Without yet implementing the above-mentioned strategies, restoration of insulin independence after single-donor islet transplantation in type 1 diabetic recipients has recently become possible on a more consistent basis. At the University of Minnesota, 13 of 15 single-donor islet recipients have attained insulin independence (9, 10). The incorporation of several strategies may have contributed to our success. We excluded pancreases from donors 50 years and higher, limited ischemic injury of islets by narrowing cold storage to less than 8 hr and by using the two-layer pancreas preservation method during the entire duration of cold storage, avoided islet-toxic reagents during islet processing, cultured islets for 2 days, initiated potent immunosuppressive and antiinflammatory treatment pretransplant, provided prophylactic anticoagulation and aggressive insulin therapy peritransplant, and minimized exposure to calcineurin inhibitors.

Achieving insulin independence with islets prepared from a single donor pancreas will undoubtedly have profound implications on the transition of islet transplants from clinical research to clinical care. Single-donor islet transplants will allow validation of islet potency assays, increase safety, reduce costs, facilitate health insurance coverage, promote donor pancreas allocation to islet recipients, and support the overall availability of islet transplants. However, implementation of islet transplants for the treatment of type 1 diabetes will require not only achievement but maintenance of insulin independence.

A substantial subgroup of insulin-independent islet allograft recipients has experienced gradual deterioration of islet graft function in years 2 and 3 posttransplant. Contributing factors are unknown. Failure of initially successful islet allografts in type 1 diabetes could be related to: 1) failure of immunosuppressive regimens to control alloimmunity and autoimmunity; 2) failure of islet regeneration in the presence of currently applied immunosuppressive regimens; and/or 3) failure of islet neogenesis in the absence of an adequate mass and viability of cotransplanted/engrafted islet precursor cells. Preliminary findings suggest a small but detectable islet beta cell pool undergoing rapid turnover in pancreas of humans resulting in the neogenesis (or replication) of 250,000 islets each year (Butler PC, personal communication, 2004). In the absence of islet regeneration at the transplant site, islet transplants may cease to function after 2–5 years. We should avail ourselves of the new thinking emerging from the work of islet regenerators before they will take over the spotlight and challenge to cure diabetes.

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