Finding a New Home for Islet Cell Transplants

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We keep moving forward, opening new doors, and doing new things, because we're curious and curiosity keeps leading us down new paths. (Walt Disney quoted from "Meet the Robinsons" 2007).

Clinical islet transplantation is the only currently available treatment for type 1 diabetes that offers a potential cure. Currently, clinical islet transplantation is performed by infusion of islets into the portal vein of type 1 diabetes patients, where the islets are exposed to numerous insults including low oxygen tension, high concentrations of endotoxin, and immunosuppressive drugs, the instant blood-mediated inflammatory response (IBMIR) as well as the insult of both recurrent alloimmunity and autoimmunity.[1] These stresses contribute to the early and high loss of human islets after transplantation, which has been estimated to result in the loss of up to 70% of the transplanted cells.[2] Intrahepatic islet transplantation presents the further disadvantage of being unable to retrieve cells after transplantation, or to perform diagnostic biopsies for allograft dysfunction or rejection. Thus, there is great need in the field for new approaches that would prevent the early cell loss and overcome the obstacles that prevent graft monitoring. One possible way forward is the development of alternative sites for islet transplantation, which could potentially provide a safer, less toxic environment for the islet cells to reside, and might potentially enable the transplant to be monitored noninvasively and potentially biopsied.

A variety of alternative sites have been proposed for islet transplantation including the omentum, skeletal muscle, under the kidney capsule, intrasplenic, and bone marrow. A subcutaneous implantation site would be desirable due to ease of implantation and retrieval of cells; however, previous studies have not met with success due in part to poor vascularization of the implant site.[3] In the past, other strategies to promote subcutaneous vascularization including implantation of biomaterials to create vascular networks have failed due to fibrosis and scar formation largely due to tissue response to the materials causing fibrosis. Recently, however, success in improving vascularisation for murine islet transplantation has been achieved within a macropolymer device implanted subcutaneously.[4]

In this issue of Transplantation, Pepper et al[5] from the Edmonton group, extend their previous studies[6] showing evidence of creation of a vascularized subcutaneous space in mice using a novel "deviceless (DL) approach" to create a prevascularized site for islet implantation and transplanting a marginal mass of islets. Two-centimeter segments of a 5-French (Fr.) textured nylon radiopaque angiographic catheter were implanted subcutaneously into the lower left quadrant of C57BL/6 mice and removed after 1 month. Subsequently, a marginal mass of murine islets (150 IEQ/mouse) was injected and transplanted into the subcutaneous prevascularized site created by the DL approach. The subcutaneous DL transplant approach promoted engraftment of marginal mass mouse islets, although this was slower than islets transplanted under the kidney capsule. Ultimately, both sites showed comparable efficacy in terms of glucose homeostasis. Islets implanted subcutaneously in the same experiments without the prevascularized space failed to reverse diabetes. Taken together with the previous studies, this current article reinforces the utility of this approach to generate an alternative vascularized extrahepatic site that supports islet transplantation. Critical to creation of the vascularized space is the removal of the catheter after 1 month, causing cessation of the foreign body response, but leaving a primed environment that facilitates the engraftment of islets. Although this new subcutaneous site supported islet engraftment, there was a delay in full engraftment in the DL animals compared with the classical kidney capsule animals, suggesting that further growth of vessels was still required after transplant in this model.

A clinically feasible extrahepatic islet transplant site has the advantage of potentially enabling transplanted cells to be easily retrieved. As a rapid translational bridge into the clinic, it is conceivable that other insulin secreting tissue, such as autologous induced pluripotent cells derived insulin-secreting tissue could be implanted into and safely retrieved from such a subcutaneous site. Furthermore, such alternative sites might also enable xenogeneic islet cells to be implanted—the potential to remove the transplanted cells would also benefit the potential clinical application of this future cell source in the event of adverse reaction, malignant transformation, or infection. Transplantation of islets, either allogeneic human or xenogeneic, into an alternative low flow nonportal vein site might also reduce risk of IBMIR, increasing the possibility of single donor islet transplantation.

Several potential disadvantages also exist with a subcutaneous implantation site. First, subcutaneous extra hepatic sites pose the theoretical risk of systemic hyperinsulinemia

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as the secreted insulin will be secreted into the systemic rather than splanchnic circulation (as occurs with intrahepatic transplantation). Second, there are concerns about the physical capacity of an extrahepatic subcutaneous site to accommodate the entire currently transplanted islet mass. Intriguingly, if a reduction in IBMIR is seen by the extraportal approach, then theoretically smaller transplant islet mass may be sufficient, mitigating this potential disadvantage. Third, the subcutaneous site is the classic site for immunization, raising the possibility that the immunogenicity of islet allograft might be increased by implantation in this site. Finally, the location may place the allograft at risk of physical trauma (eg, abdominal wall implantation or upper arm) and potentially thermal injury in either excessive high or low temperature that might impair allograft function.

How such a subcutaneous site might behave clinically needs to be tested in large animals now, where the pros and cons of this promising approach may be explored before potential transition to the clinic. Finally, as an aid to current intraportal islet transplantation, the development of a subcutaneous alternative islet transplant site raises the possibility of a sentinel graft being created synchronously with classic intraportal islet transplantation. Such a sentinel graft would be amenable to noninvasive monitoring and biopsy for the diagnosis of graft dysfunction.

Thus, driven by curiosity, Pepper and the team in Edmonton have moved the field of islet transplantation forward, opened a new door into a potential subcutaneous space, and led us down a new path to a potential alternative site for islet cell transplantation.

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