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INVITED COMMENTARY

Pharmacologic strategies for improvement of islet survival: targeting the enterohormonal axis*

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The adequacy of insulin secretion following both allogeneic and autologous islet transplantation is related to the number of islets transplanted into recipients. Achieving insulin independence in diabetic patients undergoing an islet allotransplant has generally required islet isolation from at least two donor pancreas grafts, or greater than 700 000 islets, while prevention of diabetes in islet autotransplant patients requires 300 000–500 000 islets [1–5]. These islet requirements are somewhat higher than would be predicted given current concepts of the pathogenesis of type 1 diabetes, whereby abnormalities in glucose homeostasis are not seen until 80–90% of the β-cells are destroyed, or given extrapolation from patients undergoing hemipancreatectomy, in whom normoglycemia is maintained with about 200 000 islets retained in the pancreas [5].

Data from recent longitudinal trials indicate that the vast majority of patients undergoing islet allotransplantation will have a progressive loss of β-cell secretory capacity over time [6]. The cause of islet cell failure posttransplant is multifactorial. During isolation, β-cell innervation and vascularization are disrupted [7]. Lack of normal vascularization, combined with a surrogate location in the liver, which has a lower concentration of oxygen than the pancreas, leads to a hypoxic condition of transplanted islets [8]. Furthermore, islets are exposed to an inflammatory cytokine milieu and must also overcome the instant blood-mediated inflammatory reaction (IBMIR) elicited by contact of isolated islets with the bloodstream [9,10]. In addition to prevailing against autoimmune and innate immune assaults, transplanted islets must withstand the toxic environment generated by immunosuppressive drugs such as sirolimus (Rapamune®) and tacrolimus (Prograf®). None of the major therapeutic modalities currently used to treat diabetes seem to arrest progressive β-cell failure and change the natural course of diabetes. Therefore, interventions that are effective in promoting islet mass would be a major advance in treating and potentially preventing diabetes.

A number of studies have focused on the actions of glucagon-like peptide-1 (GLP-1), which is released from intestinal L cells and stimulates insulin secretion, promotes β-cell regeneration, and prevents β-cell apoptosis [11,12]. Its antidiabetic actions, however, are short-lived: after being secreted, GLP-1 is rapidly degraded by

dipeptidyl peptidase-4 (DPP-4). In a study described earlier this year in *Transplant International*, Lei Tian, Jie Gao, and colleagues demonstrated that exendin-4, a GLP-1 analog with a longer half-life, improved islet graft function in both mice and humans [13]. They also demonstrated that exendin-4 stimulated β-cell replication, though, in human tissue, such stimulation was limited to islet grafts from young (≤22 years) donors.

In the last issue of *Transplant International*, these same authors, Jie Gao, Lei Tian, and colleagues present their discovery of a novel approach to increasing β-cell mass and enhancing islet graft function, through use of G-protein-coupled receptor 119 (GPR119) agonists (*Transpl Int* 2011; 24: 1124). GPR119 is expressed in β-cells and intestinal L cells, and its agonists have previously been shown to promote insulin and GLP-1 secretion [14,15]. The article in this issue establishes that GPR119 agonists improve islet graft function in mice, and stimulate replication of β-cells, both *in vitro* and *in vivo*. Furthermore, they increase the plasma concentration of active GLP-1 in mice, thereby possibly enhancing insulin secretion and β-cell regeneration indirectly, as well as directly. Given the effects of both GPR119 agonists and GLP-1 on insulin secretion and on β-cell regeneration, a two-pronged approach that combines the use of GPR119 agonists and DPP-4 inhibitors may prove even more successful than the use of either treatment alone.

GPR119 agonists are emerging as a very promising therapeutic approach for the treatment of type 2 diabetes as well [16,17]. Because GPR119 was discovered relatively recently by several groups, it has been referred to by different names, such as glucose-dependent insulinotropic receptor (GDIR) and RUP3. GPR119 agonists stimulate glucose-dependent insulin secretion *in vitro* and also lower elevated glycemic levels *in vivo*. In addition, they stimulate the release of incretins, such as GLP-1 and gastric inhibitory polypeptide (GIP) [18]. Several companies have obtained patents describing GPR119 agonists and have advanced them to the clinical arena of type 2 diabetes treatment [17]. They have discovered the great potential in the development of small molecule compounds that stimulate GLP-1 secretion.

Aside from holding promise for diabetic patients undergoing islet allotransplantation, the above findings have the potential to improve outcomes in chronic pancreatitis (CP) patients undergoing islet autotransplantation. One of the challenges of autotransplantation is that physicians often use it as a last resort, after patients have undergone a partial pancreatectomy and thus have a reduced number of islets. Moreover, achieving a high yield of islets from the patient's own diseased pancreas can be difficult, sometimes impossible, particularly if the organ displays a high degree of fibrosis and calcification, as is common in late-stage CP. Islet autotransplants, despite their lower transplanted β-cell mass, have a higher rate of success than islet allotransplants; however, only 47% of islet autotransplant recipients are still insulin-independent 5 years posttransplant, so there is still room for improvement [19]. If GPR119 agonists prove to be as successful at stimulating insulin secretion and β-cell replication in human islet grafts as in murine islet grafts, the insulin-independent rate at 5 years posttransplant could possibly be increased.

In conclusion, the islet transplant community remains vitally interested in continuing to investigate the biochemical and molecular basis for beneficial insulin secretory and blood glucose-lowering actions of incretin mimetics, GLP-1 analogs, and DPP-4 inhibitors. Ongoing efforts are devoted to understanding the complementary roles of islet transplantation and GPR119 agonists in the potentiation of glucose-stimulated insulin secretion.

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