Survival of the Fittest? Natural Selection in Islet Transplantation

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The full potential of cadaveric islet transplantation will only be realized by avoiding both pretransplant insults programming islets for subsequent death and posttransplant triggers for apoptosis and necrosis. The immediate blood mediated inflammatory response causes significant islet loss in the immediate posttransplant period. However, if we focus on this alone we will miss many opportunities to improve transplanted islet survival. Even when single donor islet transplants become the norm, there will still be more patients who might benefit from islet transplants than grafts available. Input from “transplanters” and diabetologists is essential in order to select appropriate patients for islet transplantation.

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The campaign to establish islet transplantation as an acceptable alternative to insulin treatment for type 1 diabetes mellitus has been waged to the point at which victory appears to be in sight. The fact that a forum such as this can consider the prospect of successful replacement therapy with islets from a single pancreas testifies to how much has been achieved. Islet transplantation has become a credible procedure. The success achieved with the Edmonton protocol (1, 2) reflects incremental improvements in many areas, including better identification of optimal donor characteristics, better organ retrieval techniques, minimization of cold ischemia times, better isolation technique and avoidance of immunosuppressive drugs which impair islet function and viability. Despite all this, islets from multiple pancreases are normally required for insulin independence. Korsgren and colleagues review the current status of clinical islet transplantation, and conclude that the major obstacle to routine insulin independence with a single pancreas is loss of islets immediately following transplantation. They argue that the immediate blood mediated inflammatory response (IBMIR) is a major contributor to this. We will compare this with the other insults that result in early islet loss and will go on to ask how islet transplantation will look as an alternative to insulin therapy when single pancreas transplants become the norm.

The immediate blood mediated inflammatory response may be said to have come of age in 2002 (3, 4) and a number of therapeutic strategies for its prevention have been proposed. Korsgren et al. present an informative and detailed theoretical analysis of the maximum potential islet yields, and conclude that experienced centres are obtaining something close to the maximum possible. It follows from this that prevention of posttransplant islet loss has become the most important goal of therapy. Whilst acknowledging the force of their argument, we believe that pancreas retrieval and islet isolation are arenas in which important victories still need to be won, and that an important element of the argument is missed by their focus on maximum yields. At present even experienced centres can obtain “clinical grade” preparations in no more than 50% of isolations, largely due to insufficient islets. The potential for improvements in this area are illustrated by the potential impact of use of the two-layer method for pancreas preservation. The two-layer method greatly improves islet yield (5, 6). A study from Edmonton found that 62% of pancreases preserved using the two layer method yielded clinical grade preparations as against only 22% of pancreases preserved in University of Wisconsin solution, as described in the original Edmonton protocol (7). The two-layer method also improves islet quality from marginal donors (8) and makes pancreatic resuscitation possible after ischemic damage (9). The two layer method is not as yet widely used, and—although unlikely to bring a major increase in the number of single pancreas transplants—its use will increase the number of patients transplanted: still a worthwhile goal.

The fate of islets in the immediate posttransplant period is not determined solely by events occurring posttransplantation. Changes in the energy status of islets and of the balance of pro-apoptotic and anti-apoptotic mediators occurring during retrieval, preservation and isolation will determine the ability of islets to resist subsequent pro-apoptotic insults: only the fittest will survive. Apoptosis may be triggered by multiple insults including inflammatory cytokines (predominantly IL-1beta, TNF-alpha, and IFN-gamma (10, 11)), metabolic stress and hypoxia. The “cytokine storm” associated with brain stem death may thus be a significant early trigger to beta cell apoptosis. Islets then undergo an inevitable period of hypoxia during pancreas retrieval, storage and islet isolation. Activation of apoptotic pathways by these insults may not be evident prior to transplantation, but may “programme” islets for subsequent apoptosis to varying degrees, depending on the severity of the combined insults. In support of this argument, islet ATP content is a marker of “metabolic health” and reduction in the ATP:ADP ratio is one indicator of the impact of such insults. The ATP content of donated pancreata varies significantly, reflecting the variability in the quality of organ retrieval and preservation prior to islet iso-
tion (12). AMP kinase is a molecule expressed in beta cells that is of particular interest as it is activated by both hypoxia and "metabolic stress". Physiologically it plays an important role in glucose sensing. However, activation of AMP kinase will be deleterious to graft function through inhibition of beta cell insulin release (13, 14) and may also trigger beta cell apoptosis through a c-Jun N-terminal kinase and caspase dependent pathway (15, 16). Further improvements in organ retrieval, organ preservation prior to isolation and islet isolation techniques should reduce programming of islets for apoptosis and improve islet survival over the first 24 to 48 hr following transplantation, when further hypoxic and inflammatory insults are received. Korsgren et al. acknowledge this. Use of the two layer method for pancreas preservation may have important benefits here also as it increases ATP content (9), and reduces islet apoptosis (17). Gene therapy, including over-expression of Bcl-2, may also prevent early apoptotic islet loss (18). Taken together, this work implies that the fate of transplanted islets is determined long before cell death becomes apparent. Further understanding of the pathways involved should lead to the emergence of therapeutic strategies which minimize islet loss.

This said, we do not dismiss the importance of the environmental insults that drive early islet loss in the immediate posttransplant period, or the importance of the immediate blood mediated inflammatory response. Reduction of islet loss from these early non-antigen specific insults will set the scene for further battles against the ongoing insults of rejection, recurrent autoimmune disease and senescence, which will also need to be won. The success of whole pancreas transplantation does however suggest that rejection and recurrent autoimmune disease can be prevented in most cases. Graft survival will be improved by new immunosuppressive strategies, but the main gain in this area will perhaps be by improved tolerance induction, freeing patients from the need for ongoing immunosuppression and the systemic toxicity this brings in its train.

Let us now assume that single pancreas transplants will become more widely used, and consider what changes this may bring. If we begin with the question of supply, data from the Swiss transplant registry suggest that 31% of multiorgan may bring. If we begin with the question of supply, data from this brings in its train.

REFERENCES


