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Death and Dysfunction of Transplanted β-Cells: Lessons Learned From Type 2 Diabetes?

β-Cell replacement by islet transplantation is a potential curative therapy for type 1 diabetes. Despite advancements in islet procurement and immune suppression that have increased islet transplant survival, graft function progressively declines, and many recipients return to insulin dependence within a few years posttransplant. The progressive loss of β-cell function in islet transplants seems unlikely to be explained by allo- and autoimmune-mediated mechanisms alone and in a number of ways resembles β-cell failure in type 2 diabetes. That is, both following transplantation and in type 2 diabetes, islets exhibit decreased first-phase glucose-stimulated insulin secretion, impaired proinsulin processing, inflammation, formation of islet amyloid, signs of oxidative and endoplasmic reticulum stress, and β-cell death. These similarities suggest common mechanisms may underlie loss of insulin production in both type 2 diabetes and islet transplantation and point to the potential for therapeutic approaches used in type 2 diabetes that target the β-cell, such as incretin-based therapies, as adjuncts for immunosuppression in islet transplantation.

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β-Cell replacement by islet transplantation offers a potential cure for type 1 diabetes. Islet transplantation can slow the progression of the devastating micro- and macrovascular complications of diabetes beyond that of best medical therapy (1). This procedure, however, is still far from ideal despite recent improvements (2). Much focus on islet loss following transplantation has centered on immune-mediated mechanisms of graft destruction. Although immune-mediated destruction of β-cells contributes to graft failure, accumulating evidence from animal studies and clinical islet transplantation suggests that nonimmune factors also play an important role. Some of these factors, notably endoplasmic reticulum (ER) stress and islet amyloid, are also thought to be important in the pathogenesis of type 2 diabetes. In this Perspectives in Diabetes article, we argue that dysfunction and death of transplanted β-cells closely resembles that of type 2 diabetes and that these similarities may have therapeutic implications for islet transplantation.

THE β-CELL IN TYPE 2 DIABETES

It is well-recognized that defects in β-cell function and mass are critical contributors to the pathogenesis of type 2 diabetes. The β-cell in type 2 diabetes is characterized by genetic and acquired defects in mass and function and gradual loss by apoptosis. First-phase glucose-stimulated insulin secretion is defective in patients with impaired fasting glucose or impaired glucose tolerance (3). In the face of insulin resistance, insulin production initially increases, but by disease onset is insufficient to compensate. Over time, β-cell function progressively declines, and eventually insulin secretion in response to glucose is nearly absent and is reduced in response to

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nonglucose secretagogues such as arginine (3). Insulin secretory patterns are also abnormal (4). Diurnal and ultradian oscillations in serum insulin concentration are decreased in humans early in the disease process due to impaired pulsatile insulin release (4). Finally, proinsulin processing is known to be impaired in type 2 diabetes. Basal and stimulated proinsulin levels and the proinsulin/insulin ratio are significantly elevated in type 2 diabetic patients (3).

In addition to progressive loss of function, β-cell mass is also lost over the course of the disease. One autopsy study suggested that β-cell volume may be reduced by as much as 40% in individuals with impaired fasting glucose and 63% in humans with type 2 diabetes at time of death (5), suggesting a role for β-cell loss in disease progression. Loss of β-cell mass in type 2 diabetes is thought to be associated with increased β-cell apoptosis, rather than decreased replication or neogenesis (5). Potential causes of β-cell death in type 2 diabetes include glucolipotoxicity, ER stress, oxidative stress, local islet inflammation, and islet amyloid (3,6,7).

THE β-CELL IN ISLET TRANSPLANTATION

Islet transplantation, a procedure in which islets isolated from pancreas of cadaveric organ donors are transplanted into the portal vein of type 1 diabetic patients, gained international recognition following the success of the Edmonton Protocol. A longitudinal survey of patients from the International Trial of the Edmonton protocol revealed, however, that following successful achievement of insulin independence, ~75% of recipients required insulin supplementation within 2 years (8). Somewhat improved results were more recently described by the Collaborative Islet Transplant registry (2), which reported rates of insulin independence of 71% at 1 year and 52% at 2 years posttransplantation in islet allograft recipients.

Surprisingly, despite requiring exogenous insulin, the majority of clinical islet transplant recipients still have detectable serum C-peptide at the time of graft failure (2,8), suggesting that loss of insulin independence is unlikely to be due simply to β-cell loss but also to β-cell dysfunction. Further, the available evidence suggests that factors in addition to immune-mediated destruction contribute to progressive graft dysfunction. Although development of islet autoantibodies following clinical islet transplantation is associated with detrimental graft outcomes (9), in the International Trial of the Edmonton Protocol (8), 82% of islet transplant recipients were autoantibody-negative at 1 year posttransplantation, at which point 40% of recipients had lost insulin independence. Toso et al. (10) failed to detect dense T cell infiltrates in biopsies from 16 human islet allograft recipients; in biopsies in which some immune cell infiltrate around islets was observed, there was no correlation with graft dysfunction even in two patients with worsening glycemic control. In three separate case reports of human islet grafts studied at autopsy (11), there was a lack of lymphocytic infiltration of islets even though these transplants were failing at time of death. In several of these case reports, there was also no increase in autoantibodies and minimal alloreactivity. A similar finding was reported for slowly progressive dysfunction of cynomolgus macaque islet allografts that were adequately immunosuppressed (12); these grafts did not demonstrate invasive lymphocytic infiltration characteristic of islet allograft rejection. Taken together, these findings make a strong case for the involvement of nonimmune factors in long-term graft dysfunction.

That nonimmune mechanisms are at play in gradual islet graft decline is further supported by data from recipients of islet autografts. Humans who receive their own islets following removal of their pancreas for pancreatitis (13), as well as primate islet autograft recipients (12), have a slow loss of insulin independence despite absence of allo- and autoimmunity. Accordingly, insulin dose typically increases each year following islet autotransplantation (14). The gradual loss of the ability of the transplanted β-cell to maintain glycemic control despite the absence of allo- and autoimmunity suggests a progressive impairment in insulin production, reminiscent of that seen in type 2 diabetes. In the following sections, we compare the defects present in transplanted β-cells to those known to exist in type 2 diabetes and make the case that the transplanted islet shares remarkable similarities with the type 2 diabetic islet.

Impaired Secretion

Like type 2 diabetic patients, islet transplant recipients demonstrate decreased first-phase glucose-stimulated insulin secretion. Human islet transplant recipients tend to have elevated fasting blood glucose compared with healthy control subjects (8,15), and loss of glycemic control in transplant recipients is progressive (8). In hyperglycemic clamp studies performed in human islet transplant recipients, both first- and second-phase insulin secretion were found to be decreased compared with healthy, immunosuppressed control subjects (15,16). Arginine-stimulated insulin secretion, glucose potentiation of secretagogue-stimulated insulin secretion, maximal secretory capacity, and glucose disposal were all reduced in these patients (15,17) as in type 2 diabetes, and this impairment worsened over time (17), suggesting a progressive decline in secretory function. Similar findings have been reported in syngeneic murine islet transplants (18), in which there are no alloimmune-mediated effects. As early as 1 week following transplantation, insulin secretion from transplanted islets was significantly lower than that of freshly isolated islets in vitro, and defects in insulin secretion became more profound at 12 and 40 weeks posttransplantation (19). Although insulin secretion from transplanted islets oscillates with a periodicity similar to that in normal control subjects (15), the pulse mass and amplitude are

reduced by 50% during a hyperglycemic clamp (15). This progressive loss of insulin secretion and glycemic control in islet transplant recipients is thus reminiscent of the natural history of type 2 diabetes, albeit over an accelerated time frame.

Impaired Proinsulin Processing

In type 2 diabetes, deficient proinsulin processing leads to increased secretion of the insulin precursors proinsulin and des 31,32 proinsulin (3). We found that the ratio of total proinsulin/C-peptide in islet allograft recipients was similar to that in a group of age- and BMI-matched type 2 diabetic patients and was elevated to 170% that of nondiabetic control subjects, suggesting that a prohormone-processing defect is present in islet transplant recipients (20). Interestingly, the proinsulin/C-peptide ratio is particularly elevated in islet transplant recipients who fail to maintain insulin independence (21–23), suggesting an association with graft failure. One study reported no difference in proinsulin/insulin ratio among islet transplant recipients, normal control subjects, and immunosuppressed recipients of other organ transplants in patients with lower HbA_{1c} and at earlier time points posttransplant (24). Taken together, these findings suggest that defective proinsulin processing may be a marker of graft dysfunction and eventual failure and may be exacerbated by hyperglycemia (25). Since immunosuppressive drugs (26) and the immune attack on islets could contribute to β-cell dysfunction in grafts, we also measured proinsulin and C-peptide in patients who received islet autografts, in which no immune-mediated defects should be present. These patients had proinsulin/C-peptide ratios several-fold higher than those of islet allograft recipients (20), suggesting that impaired prohormone processing is intrinsic to the transplanted islet. Unlike most islet allograft recipients, however, autograft recipients receive islets from a single pancreas; thus, the greater defect in proinsulin processing may in part be secondary to increased secretory demand associated with a suboptimal transplanted islet mass. Regardless, the presence of increasing proinsulin/C-peptide ratios in islet autograft recipients is indicative of an intrinsic and progressive processing defect in islet transplants.

β-Cell Mass in Islet Transplants

Progressive loss of β-cell mass is a key contributor to type 2 diabetes pathogenesis. In islet transplantation, the islet mass obtained from a single donor (several hundred thousand islets) is usually insufficient to normalize blood glucose. The number of islet equivalents (IEs) is calculated from the diameter and number of islets, although recent work has questioned the validity of this measurement and whether it may overestimate true functional β-cell volume (27). Nonetheless, based on this widely used clinical measure, graft function and survival is considered to be optimal when a recipient receives >10,000 IEs/kg, typically requiring pancreata from multiple donors (8). Current islet isolation protocols do not recover the entire pancreas' worth of islets, and islets are further lost in pretransplantation culture and following infusion. Thus, from the outset, islet transplant recipients likely have insufficient β-cell mass, since they receive less than the islet complement of one normal pancreas, at least until they receive a second or third islet infusion. A critical number of islets is required to attain glycemic control (8,20,22). Patients who receive <10,000 IEs/kg have impaired β-cell function relative to those receiving >10,000 IEs/kg (20). In animal models, transplantation of a marginal mass of islets predisposes recipients to defective glucose-stimulated insulin secretion and poorer glycemic control (22,28). Clearly, long-term glycemic control requires a critical islet mass. A recent report of subjects undergoing pancreatic surgery suggested that the threshold after which diabetes develops is a loss of ~65% of β-cell mass (29).

As in type 2 diabetes, loss of islet transplant mass is progressive. In vivo imaging demonstrated slowly progressive graft loss over 4–6 weeks in human islets transplanted into immune-deficient mice (30). Imaging of autologous rat islet transplants suggests a similar trend (31). Magnetic resonance imaging studies of human islets transplanted into human recipients suggest 2 phases of islet mass loss: a 60% decrease in engrafted islet mass during the first week and a subsequent slow decline over months (32). Consistent with this decrease in mass, apoptotic islet cells were detected in marginal mass human islet grafts in immune-deficient, diabetic mice (22).

Importantly, loss of transplanted β-cells likely contributes to worsening transplant function and further graft mass decline, as may be the case in diabetes. Defective glucose-stimulated insulin secretion (28) is observed when fewer islets are transplanted in animal models. We found that the proinsulin/C-peptide ratio was higher in human allo- and autograft subjects receiving <10,000 IEs/kg than those receiving more, suggesting that graft function is worse when there is greater secretory demand on transplanted β-cells (20). The proinsulin/C-peptide ratio was also reported to be higher in nude mouse recipients of 1,000 human islets as compared with those that received 2,000 islets (22). Thus, limited transplanted islet mass and progressive loss following transplantation likely aggravate graft β-cell dysfunction.

CAUSES OF β-CELL DYSFUNCTION AND DEATH IN TRANSPLANTED ISLETS AND TYPE 2 DIABETES

Glucose Toxicity

Elevated blood glucose likely contributes to β-cell loss and dysfunction in islet transplantation, as in type 2 diabetes. Prolonged hyperglycemia leads to β-cell dysfunction via glucotoxicity (and in combination with elevated lipids, glucolipotoxicity), possibly due to ER and/or

oxidative stress associated with continual glucose stimulation and by inducing islet inflammation (6). The presence of hyperglycemia in recipients at time of transplantation greatly impairs graft survival and function (33). Glucotoxic injury to β-cells may persist, as human islet grafts in immune-deficient mouse recipients that were initially hyperglycemic and normalized after 2 weeks retained defects in glucose-stimulated insulin secretion (34). Short-term insulin administration to rest β-cells and minimize hyperglycemia following syngeneic islet transplantation in mice (33) or human islet autografts (14) improves long-term graft function (14,33), preserves β-cell mass (33), and may increase β-cell replication (33). Hyperglycemia also adversely affects other islet cells, including the islet endothelium (6), as well as promoting proinflammatory changes in monocytes (35).

Islet Amyloid

Amyloid formation, a characteristic pathology of the islet in type 2 diabetes, occurs rapidly in transplanted islets. Westermark et al. (36) first described amyloid deposition in human islets 2 weeks after transplantation into diabetic, immune-deficient mice. We showed that amyloid deposition in transplanted human islets is associated with hyperglycemia in mouse recipients (37). Islets from transgenic mice with β-cell expression of human islet amyloid polypeptide (IAPP or amylin), the major component of islet amyloid, rapidly develop amyloid following transplantation into syngeneic, diabetic recipients and fail to maintain normoglycemia (38). A recent case report described amyloid deposition in transplanted islets in liver sections taken at autopsy from a human islet transplant recipient who had a marginally functioning graft at time of death (39). Amyloid was not present in the transplanted islets at the time of infusion, but was extensive at the time of analysis. Aggregates of IAPP also contribute to inflammation in transplants of human IAPP-expressing transgenic mouse islets by attracting and activating macrophages in the graft (7). Collectively, these findings suggest that amyloid forms rapidly in islet transplants and may contribute to graft failure. Inhibitors of IAPP aggregation (40) and synthesis (41) may lessen β-cell demise in type 2 diabetes and have been shown to enhance human islet survival in culture. These data raise the possibility that such an approach may also have therapeutic utility in islet transplantation.

Inflammation

As in type 2 diabetes, proinflammatory cytokines and infiltrating innate immune cells likely have detrimental effects on β-cell function and survival following islet transplantation. Syngeneic murine islet grafts express high levels of cytokines and chemokines (42). Chemokines secreted by resident macrophages, ductal cells, and damaged β-cells attract host macrophages to the graft. Some of the causes of inflammation in islet transplants appear to be shared with type 2 diabetes, such as hyperglycemia and IAPP. IAPP aggregates, which form rapidly in transplanted islets, promote proinflammatory cytokine and chemokine release by macrophages, dendritic cells, and islets in vitro (7,43), an effect that is amplified by interleukin-1 (IL-1) signaling. Consistent with the idea that IAPP aggregates promote islet chemokine release, transplanted islets from human IAPP-expressing transgenic mouse donors attract more macrophages to the graft site than do those from nontransgenic mice (7). Other potential causes of inflammation in islet transplantation include hyperglycemia, islet isolation and culture, the transplantation procedure, and ischemia-reperfusion injury. Immediately upon transplantation, tissue factor and monocyte chemotactic protein-1 exposed on the islet surface promote the instant blood-mediated inflammatory reaction (IBMIR). IBMIR is characterized by activation of the coagulation and complement systems, rapid activation and consumption of platelets, and subsequent inflammation and leukocyte infiltration. IBMIR may underlie loss of up to 60% of transplanted graft mass in the first week following transplantation (44). Thus, the proinflammatory environment in islet transplants likely contributes to β-cell dysfunction, as in type 2 diabetes. The lack of significant lymphocytic infiltration reported in failing islet transplants (as described above) despite immune suppression does not rule out the possibility of a localized immune response mediated by innate immune cells. In islet inflammation in type 2 diabetes, the number of macrophages per islet is still very low (35), although just a few islet macrophages can express high levels of proinflammatory cytokines. It is unlikely that current immune-suppressive regimens, which are designed to target allograft rejection mediated by adaptive immune responses, are sufficient to suppress innate immune responses in islet transplantation, although the role of the innate immune response in chronic graft failure requires further investigation (44).

Oxidative and ER Stress

Human islets in type 2 diabetes exhibit features of oxidative and ER stress (6). Many factors in the islet transplantation procedure and transplantation environment may promote similar stress responses in islets, including islet isolation and culture, metabolic stress, amyloid production, and inflammation. Enhanced antioxidant capacity (45) improves transplantation outcomes in animal models. Following transplantation into nude mice, human islets demonstrate expression of markers of ER stress, particularly in hyperglycemic recipients (46). In syngeneic islet grafts into either normoglycemic or diabetic rat recipients, C/EBP homologous protein (a proapoptotic mediator of both ER and oxidative stress responses) was elevated following transplantation (47), whereas in human islets transplanted into nondiabetic mice, an increase in the expression of protective, but not proapoptotic, ER stress genes was observed (48).

Increased metabolic demand on suboptimal islet transplants may increase ER stress. These stress responses and their downstream proapoptotic mediators are potential therapeutic targets to minimize β-cell death and dysfunction in both islet transplants and type 2 diabetes.

DIFFERENCES BETWEEN TYPE 2 DIABETES AND ISLET TRANSPLANTS

While there are clearly many similarities shared by β-cells in type 2 diabetes and islet transplants, there are also a number of important nonimmune contributors to β-cell dysfunction and failure that are unique to each condition. First, it should be kept in mind that while a number of different genes are thought to confer susceptibility to β-cell dysfunction and loss of mass in type 2 diabetes, these genetic defects are less likely to be present in islets isolated from nondiabetic donors. It follows that β-cell stressors present in the transplant recipient are more likely than genetic factors to contribute to graft dysfunction, although diabetes susceptibility genes in donor islets should be considered. Second, insulin resistance is an important factor contributing to β-cell stress and ultimately failure in type 2 diabetes by increasing secretory demand on the islet. While the degree of insulin sensitivity in transplant recipients likely impacts graft function, insulin resistance is not a major characteristic of islet transplant recipients as it is in type 2 diabetes, particularly since corticosteroids are not included in the Edmonton Protocol (8). Third, current immunosuppressive regimens to prevent islet allograft rejection, which are of course unique to islet transplantation, use drugs that are known to have toxicity to β-cells. For example, tacrolimus may cause post-transplantation diabetes in allograft recipients, and sirolimus may also have detrimental effects upon β-cell function (26). Fourth, revascularization is an important early event in islet transplant engraftment and survival. In type 2 diabetes, although islet endothelium and blood flow changes may impact β-cell function (49), a complete vascular remodeling does not occur as in islet transplants. Similarly, transplanted islets also lose the complex autonomic innervation present in the intact pancreas. Finally, transplantation into the hepatic microenvironment may predispose islets to dysfunction, in which β-cells will be exposed to high local concentrations of glucose and liver metabolites. Insulin content, glucose-stimulated insulin release, insulin biosynthesis, and glucose oxidation rate are markedly decreased in islets transplanted to the liver (50). Research into alternative transplant sites should continue to optimize islet engraftment and function in the transplantation environment.

ARE PREDIABETIC ISLETS DESTINED TO FAIL?

A number of characteristics specific to islet donors may influence transplant outcomes; for example, increased donor age and obesity likely predispose grafts to dysfunction. Although no data exist for islet transplantation, pancreas transplantation outcomes provide insight into the impact of donor age and BMI. Advanced donor age and higher BMI have poorer outcomes in pancreas transplantation; such donors are more likely to be allocated for islet rather than pancreas transplantation (51). Indeed, there may be a preference in islet transplantation to use such donors because digestion time is reduced and islet yield is increased. Although no clinical studies have examined the function of islets from prediabetic donors in transplantation, the transplantation of type 2 diabetic human islets fails to reverse hyperglycemia in mice (11), and donor hyperglycemia is associated with poor outcome following pancreas transplantation (51). It is plausible that islets from obese donors who would not have gone on to develop diabetes may have enhanced function (in addition to larger size), whereas those from prediabetic obese donors have acquired or genetic islet defects that make them more likely to fail. Collectively, these findings suggest that selection of donor organs for islet transplantation may be biased toward islets that are more likely to fail.

THERAPEUTIC IMPLICATIONS: WILL DRUGS USED IN THE TREATMENT OF TYPE 2 DIABETES IMPROVE ISLET TRANSPLANT OUTCOMES?

We have described a number of similarities in β-cell dysfunction shared by type 2 diabetes and transplanted islets. It follows that therapeutic approaches that promote β-cell function and survival in type 2 diabetes may also be beneficial in islet transplantation. As an example, sulfonylureas improve insulin secretion in transplanted islets (52), although it is possible that continual secretory stimulation may promote β-cell exhaustion and enhance amyloid deposition. Incretin mimetics and dipeptidyl peptidase-4 inhibitors are increasingly used for the treatment of type 2 diabetes and are thought to inhibit β-cell apoptosis and enhance proliferation. Treatment of human islet allograft recipients with exenatide significantly reduces insulin requirements and may prolong insulin independence (53). Incretin-related therapies are likely to be increasingly used in clinical islet transplantation in coming years.

β-Cell rest by insulin therapy or insulin sensitizers has been proven effective in prolonging β-cell function in clinical trials for type 2 diabetes. Importantly, the beneficial effects of insulin are sustained following cessation of insulin therapy (14,33). Insulin treatment during the peritransplant period allows glycemic normalization of marginal grafts (54) and may promote expansion of transplanted β-cell mass. Treatment with diazoxide to rest β-cells by suppressing insulin secretion was shown to be beneficial following syngeneic islet transplantation (55). The insulin-sensitizer metformin, however, has not been found to improve outcomes in islet transplant recipients (56). Nonetheless, it remains plausible that short-term β-cell rest of transplanted islets may prove

beneficial in increasing graft longevity, particularly during early engraftment, and in restoring function in marginally functioning grafts. Thiazolidinediones provide a potential therapeutic alternative to β-cell rest, given their combined effects of improving insulin sensitivity and lipid metabolism, reducing inflammation, and promoting β-cell function. Indeed, troglitazone was found to improve glycemic normalization in marginal mass islet transplants in rodents (57). This class of drugs is unlikely to be widely used in clinical islet transplantation, however, since their use is declining in type 2 diabetes due to reported adverse effects.

Inflammation is increasingly recognized as integral to the progression of type 2 diabetes and reduction of inflammation improves glycemic control in animal models and humans (58). IL-1 signaling blockade has been demonstrated to improve glycemic control and β-cell function in type 2 diabetes (59), and we have shown recently in an animal model that treatment of islet graft recipients with IL-1 receptor antagonist promotes graft survival and function, particularly in islet grafts expressing a human IAPP transgene (7). This and other anti-inflammatory therapies have great potential to improve both islet engraftment and long-term graft function (60,61).

We propose that other strategies in development for the treatment of type 2 diabetes merit strong consideration to enhance islet graft function and survival following transplantation. As an example, we have demonstrated that silencing of human IAPP expression (41) and treatment of human islets with inhibitors of IAPP aggregation protect against amyloid toxicity in vitro (40); this approach has therapeutic implications for both type 2 diabetes and islet transplantation. We have also demonstrated that cholesterol accumulation in the β-cell has a detrimental impact on β-cell function (62). As immunosuppressive agents such as sirolimus alter lipid homeostasis, emerging strategies to treat hyperlipidemia and hypercholesterolemia in the metabolic syndrome may also have value in islet transplantation. New treatments that preserve or enhance β-cell function in combination with immunosuppression could not only prolong graft survival but might also enable decreased concentrations of immunosuppressive drugs to be effective.

CONCLUSIONS

Islet transplantation is a promising and potentially curative therapy for type 1 diabetes, yet slowly declining graft function is a major impediment to its widespread clinical application. The transplanted islet has many similarities to the type 2 diabetic islet and prodiabetogenic factors in the transplant environment may further exacerbate a type 2 diabetes–like phenotype. We believe that factors independent of the allo- and autoimmune response make a major, and somewhat unappreciated, contribution to islet graft failure and that therapeutic approaches that target nonimmune contributors to death and dysfunction of β-cells in islet transplants should be pursued aggressively. The use of insulin and other therapeutic agents used in type 2 diabetes treatment including insulin sensitizers, incretin-related therapies, and other emerging approaches should be tested alone and in combination in clinical trials as a means to slow graft loss and preserve function. Prodiabetogenic factors present during islet isolation and posttransplantation should be minimized. Regarding the transplanted β-cell as a type 2 diabetic β-cell, and treating it as such in conjunction with appropriate immunosuppressive therapies, may prolong graft survival and function.

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