Islet Transplantation: An Update

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Islet transplantation offers a physiological approach for precise restoration of glucose homeostasis, thereby reversing the metabolic and neurovascular complications of diabetes. In the past, there were only a few successes with human islet transplantation and the initial results were very disappointing. However, recent reports of great successes in islet transplantation have renewed the interest in it as a possible therapeutic option for patients with type 1 diabetes. Scientists have been focusing on methods to improve the outcome of islet transplantation. The shortage of human donor pancreata has led to many efforts to expand the human donor pool, modify islet processing and preservation methods, and search for alternative islet sources. To solve the problems of islet engraftment, treating recipients during the peritransplant period with additional islets, exogenous insulin, hyperbaric oxygen, pentoxyphylline, 15-deoxyspergualin, pravastatin and nordihydroguaiaretic acid have all shown to be beneficial for the islet grafts and transplantation results. Immunomodulation and immunoisolation of donor cells have been used to overcome immunological problems, and recently, newer immunosuppressants and agents to induce tolerance have also become available. Patients with successful islet transplantations showed near normal glycemia with no hypoglycemic episode. These patients exhibited normal hepatic glucose production and improved tissue glucose disposal, despite the persistence of blunted first phase insulin peaks. The transplantation-related complications involved primarily the procedure itself and the drugs used for immunosuppression. In conclusion, islet transplantation will become a routine treatment in clinical practice once more islet sources and safer forms of immunosuppression are obtained. *(Chang Gung Med J 2004;27:1-15)*

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Progressive loss of insulin secretion caused by an autoimmune process that destroys pancreatic β-cells in genetically susceptible patients heralds a lifelong dependence on insulin therapy. Despite careful treatment, half of type 1 diabetic patients suffer from chronic neurovascular complications. Evidence indicates that these microangiopathic lesions are secondary to imperfect control of glycemia. In 1993, the Diabetes Control and Complications Trial clearly showed that intensive insulin therapy with a decrease in glycated hemoglobin significantly reduced the risk of microvascular complications.[1] However, the improvement in glycemic control was associated with a 3-fold increased risk of severe hypoglycemia and did not completely avoid chronic diabetic complications. An attractive alternative is to transplant insulin-producing tissue, either the whole/segmental pancreas or isolated islets, which can offer a more physiological approach for precise restoration of glucose homeostasis, thereby reversing the metabolic and neurovascular complications of diabetes.

Compared with vascularized pancreatic grafts,

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transplantation of isolated islets is more physiological and offers a number of advantages including, it is simpler and safer for the recipient, it can be repeated several times, islets can be tested and manipulated before implantation, and islet banking can be performed using cryopreservation. Thus, it is an ideal approach to cure diabetes. To accomplish islet transplantation, a healthy pancreas removed from a recently deceased donor is digested by collagenase; the islets are then separated from other pancreatic cells using density gradient. Finally, the islet cells are injected into the portal vein of the patient's liver and lodge in very small branches within the liver where they can sense blood glucose and secret insulin. In recent years, remarkable progress has been made in clinical islet transplantation, although some problems remain to be solved.

I. CURRENT STATUS OF ISLET TRANSPLANTATION

From 1893 through 2000, a total of 493 adult islet allotransplantations were performed at 51 institutions worldwide, mostly in North America and Europe.[2] The majority of these grafts were combined islet-kidney transplants. The total number of diabetic patients reported to be insulin independent for (1, 3, 6, 12, 24, 36, 48, and 60 month(s) was 13.4, 12.6, 11.0, 8.1, 4.5, 2.2, 1.2, and 0.4%, respectively. The longest functioning human islet autotransplant has maintained normoglycemia for more than 13 years.[2] In 237 C-peptide negative patients with type 1 diabetes mellitus who received adult islet allografts from 1990 through 1999, 1-year patient and graft survival (as defined by basal C-peptide ≥ 0.5 ng/ml) rates were 96% and 41%, respectively, and 11% of the recipients were insulin independent at 1 year after grafting.[2] Establishment of insulin independence was largely facilitated when islets were isolated from pancreata with a mean preservation time ≤ 8 hours; ≥ 6000 islet equivalents (standardized to the volume of an islet 150 μm in diameter) per kg body weight of the recipient were transplanted; and induction immunosuppression was comprised of monoclonal or polyclonal T-cell antibodies, or antibodies against interleukin(IL)-2 receptor epitopes. Additionally, islet transplantation into the liver via portal vein injection/infusion was shown to be advantageous.

Recently, Shapiro and his colleagues reported a 100% cure rate for type 1 diabetes with their "Edmonton protocol" for islet transplantation.[3] This major breakthrough has caused a groundswell of enthusiasm. In this clinical series, seven recipients without end-stage renal disease received islet grafts alone with no previous or simultaneous transplantation of kidney or other organs. Selection of recipients was based on recurrent severe hypoglycemia or metabolic instability that did not respond to treatment with exogenous insulin. Key innovations comprised the use of an immunosuppressive regimen combining daclizumab (anti-IL-2 receptor monoclonal antibody), sirolimus, and tacrolimus without corticosteroid therapy. In addition, cold ischemia time was kept short, islets were grafted fresh, and the mass of transplanted islets exceeded 9000 islet equivalents per kg of body weight of the recipient. In order to reach this mass, islets were isolated from 2 to 4 donor pancreata and transplanted sequentially. Remarkably, the majority of the recipients were discharged from the hospital within 24 hours after islet transplantation. The subsequent report from the Edmonton group was that 15/15 consecutive recipients had achieved insulin independence, with 12

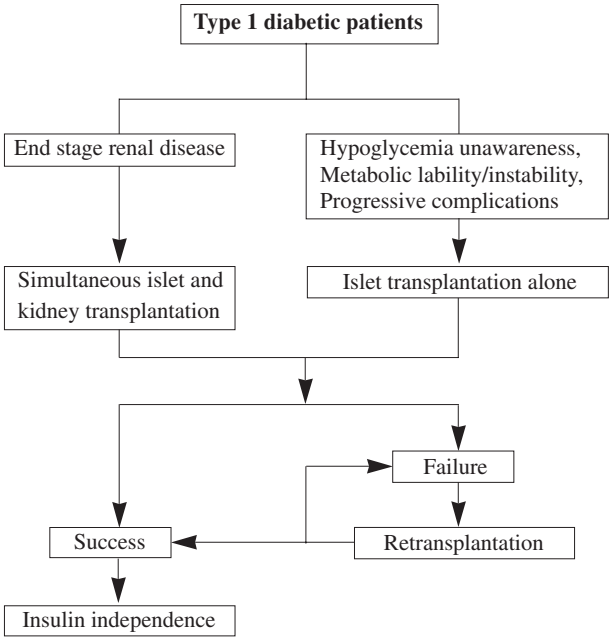

Fig. 1 The flow chart of islet transplantation for the treatment of type 1 diabetic patients.

(80%) patients remaining off-insulin with at least 1 year of follow-up after the initial transplant.[4] The clinical data demonstrated for the first time in the history of islet transplantation that persistent islet function and insulin-independence rates could be equivalent to results previously observed only in patients after transplantation of vascularized pancreas. The flow chart of islet transplantation for the treatment of type 1 diabetic patients is shown in Figure 1.

II. EFFORTS TO ACHIEVE SUCCESSFUL ISLET TRANSPLANTATION

As mentioned above, the success rate of insulin independence is very low after islet transplant from a single donor. Even in the Edmonton trial, although the insulin requirements decreased after the first transplant, it was after repeat transplant(s) that patients became free from insulin therapy. The reasons for islet allograft failure may include both non-immunological (insufficient β-cell mass and problems related to islet engraftment) and immunological (immune rejection, toxicity of immunosuppressants and autoimmune recurrence) factors. To improve the outcome of islet transplantation, scientists have been focusing on the following three methods (Table 1).

A. Transplantation with a sufficient amount of islets

The shortage of human donor pancreata has led to many efforts to expand the human donor pool, modify islet processing and preservation methods, and search for alternative islet sources, including animal islet tissues, insulin-producing cell lines, genetically engineered insulin-producing cells and progenitor/stem cells. These exciting studies hold the promise to provide available β-cells for future transplantation.

1. Expansion of human donor pool

a. Older donors

As the life expectancy of our society continues to grow, those over the age of 60 years constitute an increasing percentage of the population and the potential donor pool. However, many donors are refused without inspection because old donor age has been considered as a risk factor and relative contraindication for transplantation.[5] To elucidate the effect of donor age on islet transplantation, we have investigated the outcomes of transplantation with

Table 1. Efforts to Achieve Successful Islet Transplantation

A. Transplantation with a sufficient amount of islets
1. Expansion of human donor pool
   a. Older donors
   b. Fetal pancreatic tissues
2. Modification of islet processing and preservation methods
   a. A two-layer (UW solution/perfluorochemical) method
   b. Pancreas perfusion with collagenase
   c. Islet culture before transplant
   d. Cryopreservation
3. Searching for alternative islet sources
   a. Animal islet tissues
   b. Insulin-producing cell lines
   c. Genetically engineered insulin-producing cells
   d. Progenitor/stem cells

B. Enhancement of islet engraftment
1. Maintain normoglycemia: additional islets, exogenous insulin
2. Increase graft oxygenation: hyperbaric oxygen
3. Improve graft microcirculation: pentoxyphylline
4. Eliminate nonspecific inflammation: 15-deoxyspergualin, pravastatin, nordihydroguaiaretic acid

C. Prevention of graft rejection and autoimmune recurrence of diabetes
1. Immunosuppression
   a. Conventional immunosuppressive drugs: cyclosporine, FK506, azathioprine, mycophenolate mofetil, steroids
   b. Newer immunosuppressants: sirolimus, daclizumab
2. Immunomodulation
   a. Islet culture in low temperature or high oxygen
   b. Antibodies against MHC class II antigens or lymphoid cells
   c. Ultraviolet irradiation of the islets
   d. Islet purification by dissociation into single cells
3. Immunoisolation
   a. Macroencapsulation
   b. Microencapsulation
4. Tolerance induction
   a. Immunoprivileged sites: testis, thymus
   b. Donor bone marrow transplantation
   c. Agents to induce tolerance: anti-CD154, CTLA4-Ig, LEA29Y, anti-CD45 RB, OKT3 antibody, FTY720, sCR1, IL-15/Fc, common gamma-chain blockade, IL-10/Fc, combined anti-CD3 immunotoxin and 15-deoxyspergualin

mouse islets isolated from different donor ages and found the islets isolated from older donors functioned well and were a potential source for transplantation.[6] Thus, the elderly should be more openly considered as potential donors in order to increase the islet source for clinical transplantation.

b. Fetal pancreatic tissues

Probably more than 2000 human fetal islet transplants have been performed worldwide, mostly in Russia and China, but few systemic data are available.[7] Data on 187 fetal islet allografts have been communicated to the Registry.[7] However, insulin independence has not been achieved in a pretransplant C-peptide negative type 1 diabetic recipient.

2. Modification of islet processing and preservation methods

Established more than a decade ago, the widely used islet processing protocol continues to lack in the capability to recover sufficient numbers of islets from a single cadaveric donor pancreas for successful transplantation. Recently, several modifications were adopted to enhance islet yield and function.

In clinical islet transplantation, prolonged cold storage in University of Wisconsin (UW) solution before islet isolation significantly reduced recovery of viable islets. Kuroda et al. developed a two-layer (UW solution/perfluorochemical) method for whole pancreas preservation.[8] This method continuously supplies sufficient oxygen to a pancreas during preservation and reduces cold ischemic injury by producing adenosine triphosphate (ATP), which maintains cellular integrity and controls ischemic cell swelling. Several studies have shown that this method significantly improved islet recovery and viability, which increased the success rate of single-donor islet transplants, extended the duration of acceptable cold ischemia, and facilitated the use of pancreata from older donors.

Effective intraductal delivery of the enzyme collagenase into the pancreas is crucial to the subsequent ability to isolate viable islets. Most clinical islet transplant centers load the enzyme into the pancreas by retrograde injection using a syringe following cannulation of the pancreatic duct. An alternative approach was introduced to perfuse the pancreas with collagenase solution via the pancreatic duct using a recirculating perfusion device system.[9] Using this procedure, the enzyme solution remains cold (4˚C) throughout the perfusion time and injection pressure is monitored and properly adjusted. The islet recovery was superior compared with the standard retrograde injection using a syringe.

Once islets are isolated, they are either immediately transplanted, cultured, or cryopreserved. In vitro culture may provide several potential advantages over immediate transplant, such as the possibility to analyze the islets' functional capacities, to further purify them from the exocrine contamination, or to manipulate them with gene therapy tools. Additionally, it offers increased patient preparation time including the possibility of the administration of immunosuppressive agents prior to transplant, inclusion of many potential recipients living far from the transplant centers and further possibility of islet transplantation to transplant centers that do not have local islet isolation facilities. However, loss of islet mass, function, and viability occur when islets are kept in standard culture media. Researchers have improved culture conditions to circumvent these problems[10] which has resulted in successful transplantation.[11] Low temperature banking to store islets before transplantation is another approach used to increase transplantable islet tissues. Cryopreservation also offers several other advantages, such as modulation of tissue immunogenicity, reduction of exocrine contaminants, and quality control for sterile and viable islets before transplantation. Using the freeze-thaw protocol, insulin independence has been achieved in patients transplanted with a combination of fresh and cryopreserved islet tissues.[12,13]

3. Searching for alternative islet sources

a. Animal islet tissues

Islet tissues from animal sources have been considered for xenotransplantation. Pigs are excellent candidates because they breed rapidly, have large litters, and exhibit morphological and physiological characteristics comparable to humans. In addition, porcine insulin is structurally similar to human insulin and has been used safely for treating diabetics for decades. Unfortunately, adult porcine islets are fragile and are difficult to isolate and maintain in culture, and fetal islets exhibit poor insulin secretory responses to glucose. Groth et al. reported that small amounts of porcine C-peptide in urine were detected in 4/10 patients transplanted with fetal porcine islet-

like cell clusters, but all needed insulin treatment after transplantation.[14] In contrast, porcine neonatal pancreatic cells secreted significant quantities of insulin in response to in vitro glucose challenge. In addition, they have the potential for growth both in vitro and in vivo, and exhibit the metabolic capacity to correct diabetes in nude mice.[15,16] However, the immunological barrier to xenogeneic graft is substantially greater than the barrier to human grafts. In addition, it is unclear whether there may be a potential problem of the transmission of porcine endogenous retroviruses (PERVs) to humans receiving such transplants.[17,18]

b. Insulin-producing cell lines

Pancreatic β-cell lines may be an abundant source for islet replacement. Murine insulin-producing cell (βTC) lines had been transformed with the SV40 T antigen to expand, which could redifferentiate when the oncogene was turned off.[19] These cells secreted high amounts of insulin, and restored and maintained euglycemia in syngeneic streptozotocin (STZ)-diabetic mice. In contrast, the transformed human pancreatic β-cell lines grew indefinitely but lost differentiated functions, particularly pancreatic hormone expression.[20] A number of manipulations were used to induce functional β-cells exhibiting glucose-responsive insulin secretion both in vitro and in vivo. However, the stored and secreted insulin was substantially below that of normal human islets.[20] In addition to the regulated insulin secretion, the immune barrier of cell lines also needs to be overcome before their application in clinical transplantation.

c. Genetically engineered insulin-producing cells

Engineering of non-β cells is ideally capable of processing and storing insulin and of releasing it in such a way that normal glucose homeostasis is maintained. Target tissues tested include liver, muscle, pituitary, hematopoietic cells, fibroblasts, and exocrine glands of the gastrointestinal tract. However, achieving glucose-dependent insulin release continues to limit the clinical application of these approaches. Recently, several studies have focused on the generation of ectopic regulated β-cells. Lee et al. used an adeno-associated virus to express a single-chain insulin analogue under the control of a glucose responsive L-type pyruvate kinase promoter in the liver.[21] The treatment of both chemically induced diabetes in rats and autoimmune diabetes in non-obese diabetic (NOD) mice resulted in permanent remission of diabetes without any detectable adverse effects on the hepatocytes. Ferber et al. introduced the rat pancreatic and duodenal homeobox gene 1 (PDX-1) into the mouse liver using adenoviral vectors and demonstrated that approximately 60% of the hepatocytes had PDX-1 expression and a few showed positive immunostaining for insulin.[22] STZ-diabetic mice treated with recombinant adenovirus had increased survival and ameliorated hyperglycemia with increased plasma insulin levels. In another study, a tumor-derived gut K-cell line was induced to produce human insulin by providing the cells with the human insulin gene using a glucose-dependent insulinotropic polypeptide (GIP) promoter.[23] Mice express this transgene produced human insulin specifically in gut K cells. This insulin protected the mice from developing diabetes and maintained glucose tolerance after destruction of the native insulin-producing β-cells by STZ.

d. Progenitor/stem cells

Ductal structures of the adult pancreas contain cells that differentiate into islets. Mouse ductal epithelial cells isolated from prediabetic adult NOD mice were grown in long-term cultures, where they were induced to produce functioning islets containing α, β, and δ cells.[24] These in vitro generated islets showed temporal changes in mRNA transcripts for islet-associated differentiation markers, responded in vitro to glucose challenge, and reversed diabetes after being implanted into diabetic NOD mice. Human ductal cells obtained from adult cadaveric pancreata also were expanded successfully in vitro and were induced to differentiate into glucose responsive islets (cultivated human islet buds, CHIBs).[25] However, there were not enough CHIBs generated to be useful for clinical transplants and the ability of these cells to restore blood glucose levels in vivo is still unproven.

Stem cells are self-renewing elements that can generate many cell types in the body. Results of recent studies have suggested that stem cells may be used to make new β-cells and, thus, will solve the problem of limited β-cell supply. A cell-trapping strategy used an introduced insulin promoter-controlled antibiotic resistance to select insulin-express-

ing cells from expanded mouse embryonic stem cells (ESCs).[26] After further expansion, these cells had nearly normal insulin content and could normalize glycemia in diabetic mice. However, this procedure gives rise to proliferating cells, and thereby potentially malignant cells, rather than mature, post-mitotic cells. In addition, approximately 40% of the animals receiving transplants developed hyperglycemia 12 weeks after transplantation, probably due to the limited life span of the implanted cell clusters. Another approach was tried using multi-step culture conditions to first select nestin-positive cells from mouse ESCs and to direct approximately 15% of these cells to form islet-like clusters.[27] Despite low insulin production, the insulin-producing cells showed insulin secretion in response to physiologically appropriate glucose concentrations. When injected into diabetic mice, these cells underwent rapid vascularization and maintained a clustered, islet-like organization. Using human ESCs in both adherent and suspension culture conditions, Assady et al. observed spontaneous in vitro differentiation that included the generation of cells with characteristics of insulin-producing β-cells.[28] These findings establish the human ESCs as a possible future source for cell replacement therapy in diabetes. Other data suggests that the functional plasticity of somatic tissue-derived stem cells might be greater than expected. Ianus et al. just demonstrated that the bone marrow-derived cells, once engrafted into the pancreatic islets of their host, exhibited markers and physiological behavior characteristic of pancreatic β-cells.[29] These cells expressed insulin, glucose transporter 2 (GLUT2) and the transcriptional factors typically found in β-cells and secrete insulin when stimulated with glucose or exendin-4. Furthermore, these cells exhibited glucose-dependent fluctuations of intracellular calcium characteristic of β-cells. Once it is accepted that cells from an adult subject can be reprogrammed to express a distinct phenotype, the existence of putative pluripotential stem cells in adult tissue will be the next step to establish. Apart from circumventing the ethical dilemmas surrounding research on embryonic and fetal stem cells, adult stem cells possess another advantage, which is that they can be obtained from the patient, thus allowing autotransplantation. Theoretical drawbacks, however, such as shorter life span, which might limit their use, have to be addressed.

B. Enhancement of islet engraftment

Previously, we showed the loss of β-cell mass and function in the islet graft at 14 days after syngeneic transplantation,[30] which was probably due to the substantial damage and apoptosis in islet grafts.[31] The recipients' hyperglycemia as well as hypoperfusion, hypoxia, ischemia/reperfusion and nonspecific inflammatory response at the transplant sites may interfere with islet engraftment.

To solve these problems, we and other researchers have used the model of syngeneic transplantation with an insufficient number of mouse islets to investigate the effects of various interventions on the growth and function of transplanted islets.[30,32-41] The results showed that during the peritransplant period treating recipients with additional islets or exogenous insulin to maintain normoglycemia,[30,33,34] hyperbaric oxygen to increase graft oxygenation,[35] pentoxyphylline to improve graft microcirculation,[36] as well as 15-deoxyspergualin, pravastatin and nordihydroguaiaretic acid to eliminate nonspecific inflammation[37-40] all had beneficial effects on the islet grafts and transplantation results. In contrast, islet culture with vascular endothelial growth factor (VEGF) before transplantation did not increase graft vasculature,[41] and posttransplant administration of gliclazide to the recipients neither enhanced graft function[42] nor influenced the outcome of islet transplantation. However, results of recent reports showed that the administration of recombinant VEGF protein with islets transplanting into the kidney subcapsular space of the diabetic rats shortened the time to normoglycemia.[43] In addition, VEGF increased the viability of engrafted encapsulated islets, and prolonged the duration of normalized glycemia in diabetic mice following transplantation.[44] Thus, local adjunction of VEGF may improve the clinical outcome of islet transplantation. These findings are of importance with respect to future application in clinical islet transplantation.

C. Prevention of graft rejection and autoimmune recurrence of diabetes

1. Immunosuppression

Conventional immunosuppressive drugs, such as cyclosporine (CsA), FK506, azathioprine,

mycophenolate mofetil, and steroids were used to prevent rejection of transplanted islets. Due to the generalized, downregulatory effects of these drugs on the function of the immune system, patients were more susceptible to infection and malignancy, while the stunting of normal growth and development precluded their use in children. In addition, CsA, FK506 and steroids have adverse effects on islet function and are capable of inducing diabetes. The side effects of continuous immunosuppression are considered to be potentially more harmful to the patient than the administration of exogenous insulin. Thus, it has limited the indications to those patients who have already received another transplantation or to those who simultaneously receive islets and an organ (generally a kidney). Recently, newer immunosuppressants have become available. The glucocorticoid-free immunosuppressive regimen, including sirolimus, tacrolimus and daclizumab used in Edmonton protocol, proved to be effective in preventing graft rejection and autoimmune recurrence of diabetes, with no apparent diabetogenic or toxic effects.[3] Current and future development of immunosuppressive protocols that use nondiabetogenic compounds could further improve outcomes of islet transplantation.

2. Immunomodulation

For the prevention of islet graft rejection, donor cells can be immunomodulated by depletion of antigen-presenting cells (APC) from islets or by methods that result in functional inactivation of APC. These approaches include in vitro culture of islets in low temperature or high oxygen, treatment of the donor islets with specific antibodies directed against the major histocompatibility complex (MHC) class II antigens or lymphoid cells, ultraviolet irradiation of the islets, and purification of the islet preparations by dissociation into single cells, followed by reaggregation into islets or obtaining purified β-cells for transplantation.[45] All of these procedures have resulted in the indefinite survival of rodent islet allografts, but use in large animal models has generally not been successful.

3. Immunoisolation[46]

Using devices to separate the islets from the immune system of the recipients, two major approaches, namely macro- and micro-encapsulation, have been studied. Both of them can undergo anastomosis to the vascular system as arteriovenous (AV) shunts.

a. Macroencapsulation

Macroencapsulation is identified as the envelopment of a number of islets within permeable macrodevices. The intravascular device is usually composed of a microporous tube that allows blood to flow through its lumen and with a housing device on its outside containing implanted tissue. The device is implanted into the vessels of the host using vascular anastomoses. Implantation of vascularized biohybrid pancreas devices containing canine islet allografts in pancreatectomized dogs resulted in insulin independence without immunosuppression in some recipients.[47] However, the complications associated with vascular prosthetic surgery, such as thrombosis, intimal hyperplasia at the venous anastomosis, defects of the device and infection, remain a serious threat. The other approach is the use of extravascular devices, which have much lower surgical risks. Insulin independence has been achieved in diabetic pancreatectomized dogs by implanting canine islets encapsulated inside cylindrical chambers fabricated from permselective acrylic membranes.[48] Subsequent clinical trials further demonstrated that macroencapsulated human islets, when subcutaneously allotransplanted into patients with type 1 or type 2 diabetes, survived at the subcutaneous site and the permselective membranes protected against both the autoimmune and allogeneic immune responses.[49] The major problem of extravascular devices is the need of an impractically large surface area to maintain a packing density of islets that allow adequate oxygenation. In addition, biocompatibility problems usually result in fibrotic overgrowth with subsequent necrosis of the encapsulated tissue.

b. Microencapsulation

More promising results have been obtained using the technique of microencapsulation, in which usually each islet is enclosed within a spherical semipermeable hydrogel membrane, such as alginate or poly-L-lysine. Their spherical microcapsules offer better diffusion capacity and are permeable to glucose and insulin, but effectively protect the β-cells against cytotoxic anti-islet antibodies and immune cells. It has been shown to allow for successful xeno-

transplantation of islet grafts in both chemically induced and autoimmune diabetic rodents,[50,51] dogs,[52] and monkeys.[53] Clinically, microencapsulated human islets embodied in arterial or AV prosthesis have been transplanted into two diabetic patients.[54] Graft function was documented in both recipients and transient insulin independence was achieved in one of them. In another study, the diabetic patient with a functioning kidney graft received double intraperitoneal transplants of microencapsulated human islets.[55] Insulin-independence was achieved at 3 months after the second transplantation. The major obstacle of microencapsulation appears to be pericapsular fibrosis after transplantation, which impedes diffusion across the membrane. Many methods have been used to eliminate factors causing pericapsular cellular infiltration, including application of pure or new types of alginate[56,57] and better technology to completely envelop the islets.[57] This progress has brought about a substantial reduction in the tissues responses against encapsulated grafts. In addition, it has been shown that the macrophages, the vast majority of cells in the capsular overgrowth, were associated with a decrease in function of microencapsulated islets.[58] Thus, transplantation of encapsulated islets in combination with administration of the agents selectively suppressing macrophages such as 15-deoxyspergualine attenuated pericapsular cellular infiltration and prolong the graft survival.[59,60] Another problem of microencapsulated islets is that small molecules, such as cytokines and other pro-inflammatory mediators can still enter the protective membranes and impair the islet function.[61] To overcome it, IL-1 receptor antagonist, which competes membrane receptors with IL-1β, has been used to protect encapsulated islets against the suppressive effects of IL-1β.[62]

4. Tolerance induction

The site of transplantation can also affect the survival of islet allografts. Implantation of islets into immunoprivileged sites, such as the testis[63] or thymus,[64] with temporary immunosuppression in rats prevented rejection of islet allograft. In testes, the presence of Sertoli cells, but not Leydig cells, was required for extended survival of the islet allografts. Thus, cotransplantation of islets and Sertoli cells has been demonstrated to extend survival of allogeneic without immunosuppression.[65] It was found that a factor released by Sertoli cells was responsible for the protection of the intratesticular islet allo- and xenografts against rejection.[66] In contrast, the maturation of T-cell precursors in a thymic microenvironment containing foreign alloantigens may induce specific immune unresponsiveness or tolerance in the recipients with resultant survival of the islet allografts. However, it would be difficult to accurately and consistently place donor islets into the atrophic thymic tissue in humans.

An alternative approach is the use of donor bone marrow transplantation to induce a state of mixed chimerism. Animals reconstituted by donor bone marrow develop donor-specific tolerance and accept subsequent tissue or organ grafts from the same donor strain. Indefinite survival of islet allografts in chemically induced diabetic rats and diabetic NOD mice has been achieved via infusion of bone marrow in the absence of cytoablation.[67,68] However, future clinical applications need to prevent the occurrence of graft versus host disease (GVHD) and GVHD-mediated inflammatory responses.[69]

The availability of reagents that interfere with key pathways in the immune response offers a solution for more selective suppression of the immune responses. Blocking co-stimulation with anti-CD154 and CTLA4-Ig has prolonged graft survival in non-human primate islet allografts[70-72] and efficiently prevented autoimmune diabetes.[73,74] LEA29Y, a novel mutant form of CTLA4-Ig with increased binding activity, produced marked prolongation of islet allograft survival in rhesus monkeys.[75] Modulation of T-cell receptor-mediated signal transduction by anti-CD45 RB monoclonal antibody has shown efficacy in preventing islet allograft rejection in murine models.[76,77] Furthermore, targeting the T-lymphocyte surface receptors CD45 RB and CD154 in NOD mice prevented islet allografts from recurrence of autoimmunity and allorejection.[78] A variety of other experimental agents could turn out to be useful. One agent used in clinical islet transplant trials was a nonmitogenic humanized Fc receptor nonbinding OKT3 antibody, which inhibits T cell activation.[79] FTY720 is an agent that displaces lymphocytes from the peripheral circulation and was effective in preventing allograft and xenograft rejection, as well as autoimmune diabetes.[80,81] The soluble complement receptor 1 (sCR1) may protect islets by inhibiting the injurious inflammatory reaction elicited by the expo-

sure of donor islets to recipient blood.[82] IL-15 is a powerful T cell growth factor (TCGF) with particular importance for the maintenance of CD8(+) T cells. Blockade of the IL-15 receptor with mutated IL-15/Fc can inhibit T-cell expansion and protect islet allograft from rejection.[83] The common gamma-chain is an essential signaling component shared by all known TCGF receptors (i.e. IL-2, IL-4, IL-7, IL-9, and IL-15). Blocking the common gamma-chain of cytokine receptors induced T-cell apoptosis and long-term islet allograft survival.[84] In other experiments, IL-10/Fc prolonged islet xenograft survival by inhibiting macrophage mediated immune responses,[85] and IL-10 gene therapy alleviated the autoimmune destruction of transplanted islets in NOD mice.[86] In addition, the operational tolerance induction, which combined peritransplant anti-CD3 immunotoxin to deplete T cells and 15-deoxyspergualin to arrest proinflammatory cytokine production and maturation of dendritic cells, was shown to protect nonhuman primate islets from rejection as well as the loss of functional islet masses.[87]

III. EFFECTS OF ISLET TRANSPLANTATION

A. Metabolic effects

Patients with successful transplantation showed a festing glycemia and glycated hemoglobin, with no hypoglycemic episode.[3,4,88,89] Not all patients had absolutely normal glucose tolerance, and some had impaired glucose tolerance. These patients had normal hepatic glucose production and improved tissue glucose disposal, despite the persistence of blunted first phase insulin peaks.[4,88-90] Even partial restoration of graft function (approximately 60% of endogenous insulin secretion) was capable of normalizing the alterations of protein and lipid metabolism, leaving glucose metabolism only moderately impaired.[91]

Surprisingly, despite prolonged stable insulin independence and near-normal glycemic control, intrahepatic islet allotransplantation did not restore hypoglycemic hormonal counterregulation in type 1 diabetics. In particular, glucagon and epinephrine responses and hypoglycemic symptom recognition were not improved by islet transplantation.[92] Although no clinically significant hypoglycemic episodes were observed in insulin-independent islet recipients, the failure to restore counterregulatory responsiveness may put transplant recipients who resume using exogenous insulin at risk for recurrent episodes of hypoglycemia.

B. Effects on diabetic chronic complications

Previous investigations of diabetic rats indicated that the maintenance of normoglycemia with islet isografts prevented or reversed early diabetic microvascular complications in the eye, kidney, and autonomic nervous system.[45] In humans, few studies with systemic data are available, and the follow-up periods of those studies were too short to say whether there were sustained long-term benefits from islet transplantation. However, one recent report demonstrated that successful human islet transplantation increased patient survival rate, lowered cardiovascular death, and improved endothelial function in type 1 diabetic kidney-transplant patients.[93]

C. Transplantation-related complications

The complications of islet transplantation are substantially lower than those of whole pancreas transplantation. The complications involved primarily during the procedure itself and the drugs used for immunosuppression. The overall safety profile of the percutaneous transhepatic portal-vein access used in the Edmonton protocol is acceptable. This approach was associated with bleeding from the liver surface and portal vein thrombosis.[4,89] The acute bleeds have been solved by the use of much less heparin with the islet infusion and a solid plug of Gelfoam after the hepatic catheterization. The peripheral portal branch vein thrombosis has not been seen in any subsequent infusions into the main portal vein. Some patients had abnormal liver function tests which resolved with time, and some had abdominal discomfort of varying intensity after their procedure.[4,89] The latter may be related to peritoneal irritation, but it subsided spontaneously.

Compared with conventional immunosuppressants, the steroid-free immunosuppression used in the Edmonton series had different but minor adverse events.[4,89] Some patients experienced tacrolimus-related deterioration of renal function, and some had increased blood pressure or serum cholesterol, ane-

mia, leukopenia, arthralgias, acne, diarrhea and mouth ulcers related to sirolimus. Daclizumab has not been associated with any major problems. Diarrhea appears to respond to cholystyramine. Mouth ulcers settled spontaneously and improved considerably after the dose of sirolimus was reduced and the capsule formulation of sirolimus was substituted for the liquid form. None of the patients have had cytomegalovirus or life-threatening infections, and so far, no post-transplant lymphoproliferative disorder or malignancy has been detected.[4,89]

IV. CONCLUSION

Islet transplantation has raised the hope for a cure for diabetes. The ultimate goal is to transplant islets early in the course of diabetes, achieve long-term function of the grafted tissue without the need for immunosuppression, and prevent the development of diabetic complications. Although the success rate for islet transplantation has markedly improved recently, the future applications in clinical practice requires more islet sources and safer forms of immunosuppression.

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胰島移植：最新進展

莊峻鍠

胰島移植以生理方式來精確調節體內葡萄糖衡定，因而可矯正糖尿病所致之代謝與神經血管併發症。人體胰島移植以往的初步結果相當令人失望，僅有少數成功的病例。但最近成功率大幅提昇的報告，使其成爲第1型糖尿病患可能的治療選擇之一。

科學家們長期專研於如何改善胰島移植的成績。人體捐贈胰臟的缺乏驅使許多研究投注於拓展捐贈人口、改良胰島分離及儲存的方法，及尋找胰島的替代來源。爲解決移植後胰島生存的問題，於移植前後給予接受者更多的胰島、外源胰島素、高壓氧、pentoxyphylline、15-deoxyspergualine、pravastatin及nordihydroguaiaretic acid 均顯示有助於胰島移植體及移植成績。胰島的免疫調節及免疫隔離已被用來克服免疫問題，近來更有新的免疫抑制劑及誘導免疫耐受性的藥物可供使用。

胰島移植成功的病人其血糖趨近正常，且無低血糖的發生。這些病人雖然無第一相胰島素分泌高峰，但其肝臟的葡萄糖製造正常，且組織對葡萄糖的利用改善。移植相關的併發症主要來自於手術本身及免疫抑制藥物。

總結，一旦有更多的胰島來源及更安全的免疫抑制方法，胰島移植將可成爲臨床例行的治療。(長庚醫誌 2004;27:1-15)

關鍵字：糖尿病，胰島移植。

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