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REVIEW

Bioartificial Pancreas for the Treatment of Diabetes

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Recent advances in islet transplantation using highly purified islets and effective immunosuppression strategies have resulted in substantial improvement in achieving insulin independence in type 1 diabetes patients. However, there are side effects from long-term immunosuppression, and transplant rejection and/or the recurrence of autoimmune attack of the transplanted islets cannot be completely prevented, even with immunosuppressive treatment. Therefore, construction of a safe and functional bioartificial pancreas (BAP) that provides an adequate environment for islet cells may be an important approach to treat diabetic patients. Various types of BAP devices have been developed and examined in animals. In this review, I introduce the previous BAP studies and our approach of BAP development.

Key words: Diabetes; Bioartificial pancreas; Pancreatic islets

INTRODUCTION

The International Diabetes Federation (IDF) has announced that the number of patients with diabetes in the world totals at least 230 million, and that the incidence rate is equivalent to 6% of the total adult population (http://www.dm-net.co.jp/calendar/2006/09/004396.php). Over the next 20 years, it is estimated that this will increase to 350 million. Diabetes has been regarded as the greatest medical issue of the 21st century. Type 1 diabetes is usually diagnosed in children and young adults, and in this type of diabetes, the body does not produce insulin. Type 2 diabetes is the most common form of diabetes. In type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin. Type 2 diabetes has been increasing significantly, but both types of diabetes have become prevalent. The increase in the incidence of diabetes has been a serious issue, particularly in developing countries. Causes of this rapid increase include environmental factors, such as excessive fat intake associated with dietary changes, lack of exercise, and delays in the development of an infrastructure for providing appropriate medical treatment. Furthermore, the increased medical cost associated with the increased number of diabetic patients has also been a threat to many countries. To overcome diabetes, it is necessary to broadly develop the following issues:

1. to broaden people's knowledge of diabetes globally;
2. to recognize the significant effect of diabetes on patients, society, and the economy;
3. to prioritize diabetes issues in the healthcare and medical fields in every country;
4. to implement measures that achieve high economic effectiveness to prevent complications from diabetes;
5. to study societal strategies for the prevention of diabetes;
6. to emphasize measures to deal with diabetes among children, pregnant women, and the elderly;
7. to strengthen research into treatments.

Therefore, this review article outlines the development of a bioartificial pancreas for diabetes treatment, which corresponds to the above-mentioned item 7.

PROBLEMS OF DIABETES

Diabetes refers to a metabolic disorder characterized by chronic hyperglycemia and has two pathogenic mecha-

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nisms. Type 1 diabetes occurs when the pancreatic beta cells that produce insulin are destroyed by autoimmunity, leading to a drastically insufficient amount of insulin within the body. Type 2 diabetes occurs when the amount of insulin secretion decreases or when hepatic or muscular cells are unable to absorb glucose efficiently due to decreased insulin sensitivity. Among the patients with diabetes, approximately 90% have type 2 diabetes. Type 2 diabetes is characterized by insulin resistance, which is seemingly derived from obesity and lack of exercise, as well as abnormal insulin secretion. Although noninsulin dependent, as the stage progresses, if abnormal insulin secretion is observed, the effects of diet regimens and oral hypoglycemic agents thus prove to be insufficient, and insulin self-injection the becomes necessary. On the other hand, type 1 diabetes refers to the most severe form of diabetes, wherein insulin secretion decreases because pancreatic beta cells are destroyed by autoimmunity. In order to prevent diabetic ketoacidosis induced by type 1 diabetes and to sustain life, insulin self-injection becomes necessary. However, the current mainstream insulin treatment is unable to control blood glucose precisely, corresponding to biological changes. Furthermore, it cannot prevent the occurrence of hypoglycemia shock, hyperglycemic attack, and the corresponding three major complications—diabetic nephropathy, neuropathy, and retinopathy—as well as a lot of long-term severe complications derived from vascular diseases. These diabetes-related diseases have been increasing as the incidence rate rises (41,42).

RECENT PROGRESS IN DIABETES TREATMENT

As recent progress in diabetes treatment, it has been expected that pancreas/pancreatic islet transplantation can be replaced with insulin treatment. Pancreas/pancreatic islet transplantation enables autoregulation of insulin secretion in accordance with subtle biological changes in blood glucose, which is an ideal treatment for diabetes. Pancreatic islet transplantation refers to a method of implanting pancreatic islets isolated from the pancreas to the recipient's liver through a portal vein. Comparing pancreas transplantation with pancreatic islet transplantation, the latter is regarded as more attractive as a treatment, as it does not require any complicated surgical techniques and is not accompanied by any complications due to the pancreatic exocrine tissue. In 2000, a study from the University of Alberta in Canada recognized insulin independence in all seven recipients of pancreatic islet transplants. Since this incidence, pancreatic islet transplantation has come to receive significant attention worldwide (37). Since this announcement of the Edmonton protocol, from 1999 to 2005, approximately 400 cases of pancreatic islet transplants were conducted in the world, and favorable quality of life (QOL) of recipients has been reported. Conversely, in contrast to the success of this type of transplant treatment, the problem of a significant shortage of donor pancreases has actually emerged. In addition, pancreatic islet transplantation requires the long-term use of immunosuppressive agents, thereby leading to a risk of various complications (11,24). No solutions have yet been found for these problems with clinical transplantation settings. Various studies have been conducted to solve these problems. One is the development of a bioartificial pancreas.

BIOARTIFICIAL PANCREAS (BAP)

BAP is a device that consists of encapsulating glucose-responsive insulin-secreting cells. Within a BAP device, oxygen and nutrition are supplied to the insulin-secreting cells encapsulated by a semipermeable membrane that serves as a septum via the membrane. Then the cells secrete insulin in response to the glucose concentration. The aforementioned immunoisolation membrane is designed to permeate substances that are essential for the cells' life, such as oxygen, nutrients, and glucose, but not to penetrate cells, antibodies, and complements that would evoke an immune reaction (Fig. 1). By encapsulating xenogenic (e.g., swine) pancreatic islets and insulin-secreting cell lines to block foreign proteins and viruses, it protects patients from infection, and it is thereby possible to solve the shortage of donors for pancreatic islet transplants that serves as a barrier against immunological defense from the host for xenogenic pancreatic islets and artificial allogenic cells. Even though islet transplantation is minimally invasive, complications including intrahepatic hematoma, portal thrombosis, and hemorrhaging have been reported in a limited number of cases. BAP holds tremendous potential to solve such

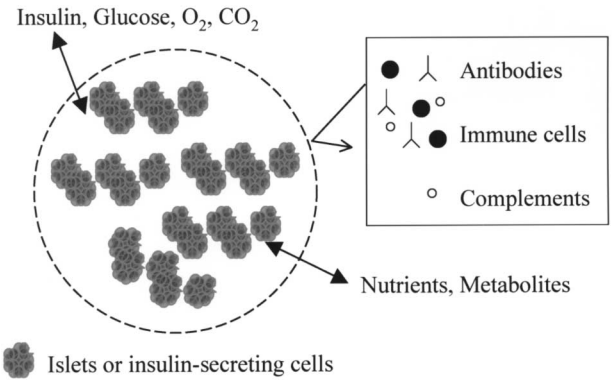

Figure 1. Schematic drawings of immunoisolation in BAP. The BAP immunoisolation system is designed to permeate substances that are essential for the cells to survive and function, such as oxygen, nutrients, and glucose, but not to penetrate cells, antibodies, and complements.

diverse problems related to islet transplantation. Therefore, there is no doubt that, to date, several studies for BAP development have been promoted throughout the world.

IMPLANTATION SITES FOR BAP

In islet transplantation, since the success of the group of Lacy in transplanting rodent pancreatic islets through the portal vein in 1973 (21), the method whereby pancreatic islets are implanted into the liver through the portal vein has also been used in current human pancreatic islet transplants. There have been some reports on animal studies regarding transplants of pancreatic islets to sites including intraperitoneal sites (6), renal subcapsules (12), spleen (13), and subcutaneous sites (20). For large animals, the results from the extrahepatic sites are not as significant as those from intrahepatic transplants through the portal vein. It has been reported that BAP can be favorably implanted in various sites including intraperitoneal, epididymis, intramuscular, subcutaneous, and other sites (9). A recent study has indicated a favorable result of implantation of BAP in the intermuscular space by using a growth factor to induce prevasculization around the BAP device (5).

TYPES OF BAP DEVICES

The types of devices for BAP have so far included microcapsules, synthetic blood vessels, and macrocapsules (Fig. 2).

Microcapsule Type BAP

The microcapsule type is intended to protect pancreatic islets by coating them with various substances to create a septum. This type of device enables the regulation of substance permeability and glucose responsiveness by changing the coating time and materials. Favorable nutrition/oxygen supply and glucose responsiveness can be expected due to the thinness of the septum of microcapsule BAP. However, the microcapsule type BAP is fragile and could be easily broken under kinetic loads within the body. In addition, considering the large surface area of each of microcapsule including islets, an extremely large space is required for BAP implantation. When any unexpected events occur after BAP implantation, it would be extremely difficult to remove the BAP. Since Lim and Sun (29) reported in 1980 that a capsule-type BAP composed of alginate and poly-L-lysine achieved control glucose levels in diabetic mice for about 2 weeks, several successful cases of BAP transplants have been reported. There has been research on polymers such as alginate-Ba^{2+}, agarose hydrogel, and alginate-L-lysine (18,28,45). Regarding alginate-Ba^{2+}, as a result of studies in nonobese diabetic (NOD) mice, the efficacy of both allogenenic and xenogenic islets as a cell source of BAP has been reported. For example, BAP using allograft transplantation achieved blood glucose control for more than 350 days in mice (10), while BAP with fetal porcine pancreatic islets controlled blood glucose levels for 140 days in mice (35). For the BAP using agarose hydorogel capsules, blood glucose control has been observed in allogenic mice for at least 100 days (23). However, for xenotransplants, it has been indicated that agarose hydorogel capsules are unable to effectively trap antibodies, complements, and cytokines, and so they cannot efficiently protect the encapsulated cells. It is essential for the success of xenotransplants to overcome the hyperacute rejection mediated by antibodies and compliments. To address the problem, a study was implemented aimed at immune isolation by mutual interference between the compliments and polyanion (17). Consequently, a method of adding polystyrene sulfonic acid, which strongly interferes with compliments, into agarose hydorogel was adopted (44). In clinical applications using human pancreatic islets, BAP utilizing alginate poly-L-lysine did not evoke any complications, and the patients became insulin independent up to 9 months later, thereby having improved QOL (38). Regarding microcapsulated pancreatic islets, in 1997, AmCyte (USA) conducted clinical studies in New Zealand using capsulated porcine pancreatic islets (14). In 2003, phase I/II clinical studies on intraperitoneal transplantation of capsulated human pancreatic islets were started in North America.

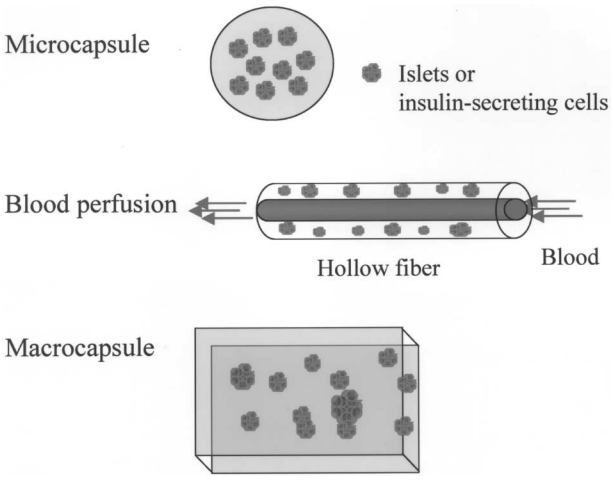

Figure 2. Three major types of BAP devices. Microcapsules, synthetic blood vessels, and macrocapsules are representatives of BAP devices.

Blood Perfusion Type BAP

For the blood perfusion type of BAP, the device is connected to an arteriovenous shunt, and the insulin-

secreting cells are cultivated in the septum within the device. This type of BAP features favorable glucose responsiveness, because the blood flow passes through the sides of the septum. It also easily permeates oxygen, nutrients, etc., advantageously. On the other hand, because surgery is necessary to connect the device to the arterial vein, invasiveness increases in comparison with other types of devices. In 1975, Chick, et al. reported an interesting blood perfusion type of BAP, wherein a device composed of a bundle of hollow fibers was connected with an arteriovenous shunt to enable the cultivation of pancreatic islet cells in the fibers (7). Such a perfusion-type device using fine hollow fibers allowed favorable glucose-responsive insulin secretion. However, it was reported that perfusion-type BAP devices were susceptible to embolism due to blood clot formation, resulting in difficulty in the long-term use of BAP (40,43). As an improved version, the same group conducted research on a device possessing coil-like hollow fibers with a diameter of 5–6 mm. When transplanting the BAP device into dogs, the concomitant use of exogenous insulin administration was still required, but more than 3 years of blood glucose level control has been achieved in allogenic transplants (39). In the case of xenotransplants in which the BAP devices were filled with porcine pancreatic islets, the result was not as favorable as that from allotransplants, but blood glucose levels were controlled for more than 8 months in dogs (31). This type of device obtained FDA approval in 1996, but it has not yet been in practical use. Multiple devices are necessary to achieve blood glucose control, and thus they increase the risk of clot formation.

Macrocapsule Type BAP

The macrocapsule type of BAP includes a diffusion chamber in which pancreatic islets are enclosed in a sac composed of two septa and a cylinder-like capsule-type device. It is advantageous that this chamber can be easily implanted into an intraperitoneal or subcutaneous space and is also easy to remove. However, the macrocapsule-type BAP causes proliferation of fibroblasts on the surface of devices over time, resulting in the decrease in nutrient/oxygen supply to the pancreatic islets and metabolite diffusing capacity. In addition, it takes considerable time to induce new blood vessels. Furthermore, when injecting pancreatic islets into the device, the pancreatic islets agglutinate, which easily leads to cell necrosis. Therefore, its glucose responsiveness is inferior to that of the microcapsule type. In 1980, Archer et al. announced another type of BAP in which pancreas islets are enclosed in a narrow cylindrical tube. After enclosing mouse pancreatic islets in a tube composed of an Amicon XM-50 membrane, a transplant was conducted in streptozotocin-induced diabetic hamsters. Blood glucose control was maintained for several months, but proliferation of fibroblasts around the device was histologically found (3). Similar findings were observed in other animal species (1,2,15). In 1991, Lacy et al. reported a subcutaneous implantation of macrocapsule typed BAP (25). Pancreatic islets were enclosed in a narrow tube with a thin membrane and approximately 60 days of blood glucose control was achieved in mice. This study clearly indicated that when pancreatic islets were injected indiscreetly, the implanted pancreatic islets agglutinated, and necrosis thereby occurred from the center of the pancreatic islets, and glucose-responsive insulin secretion decreased due to the increased size of pancreatic islets. As a result, long-term effects of transplanted islets were not obtained.

In order to solve this problem, efforts have been made to maintain cell performance by encapsulating the transplanted pancreatic islets in alginate hydrogel to prevent islets from encroaching upon each other and agglutinating. The results showed that proliferation of fibroblasts was observed in isolation membranes with small pores, whereas less proliferation of fibroblasts occurred around isolation membranes having relatively large pores and a smooth surface (27). It was also reported that the allotransplant experiment in dogs using an XM-50 membrane device achieved more than 60 days of blood glucose control (26). In the subcutaneous BAP transplant, less angiogenesis and resultant graft deficiency were noted.

It was reported that implanted pancreatic islets in the device was improved after inducing angiogenesis (19). Another report stated that 100 days of blood glucose control was achieved in diabetic mice by administering subcutaneous injection of basic fibroblast growth factors (bFGF) prior to BAP device implantation (36). Intraperitoneal transplants of mouse insulin-secreting MIN6 cells harboring sandwich-type BAP with a silicon ring septum achieved 50 weeks of blood sugar control in diabetic rats (34).

Various types of BAP devices have been studied, and the animal experiments have so far achieved only short-term success.

OUR STRATEGY FOR BAP DEVELOPMENT

We are now developing a BAP device in collaboration with Kuraray Medical Inc. (Tokyo, Japan) by adopting a dialysis technique. We have focused on the use of polyethylene-vinyl alcohol (EVAL) membrane, which is based on studies of an insulin nonabsorptive property assay (16). As shown in Figure 3, it is important to design the pore size of hollow fibers with consideration of blood cell sizes as well as molecular weights/sizes of the main important molecules and insulin. We also used unwoven polytetrafluoroethylene (PTFE) fabric in which

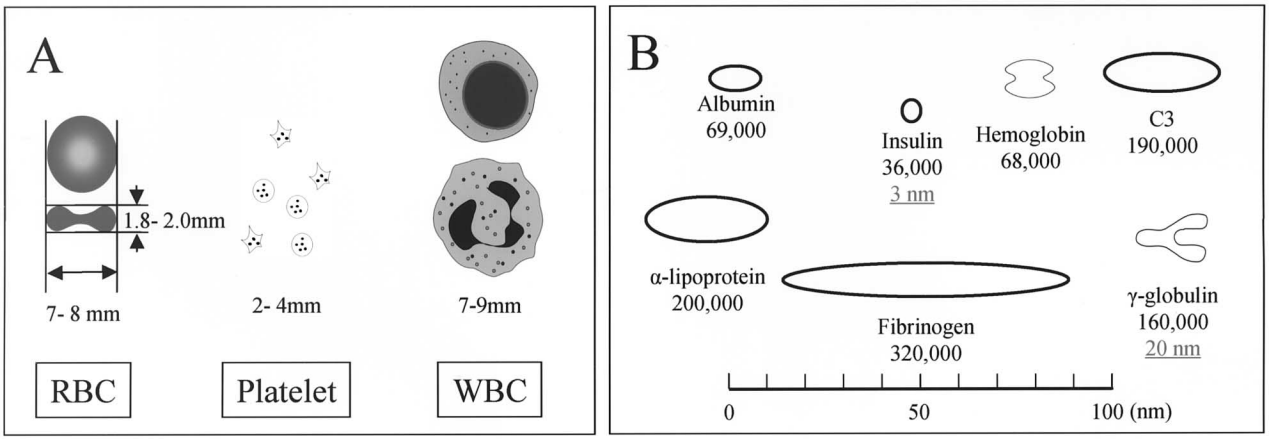

Figure 3. Molecular weights/sizes of the main important molecules and insulin. It is essential to design the pore size of hollow fibers according to blood cell sizes and molecular weights/sizes of the main important molecules.

the surface was processed with polyamino urethane in order to provide cells with an appropriate scaffold. We created an external whole blood perfusion type of BAP using porcine pancreatic islets as a cell source. In an experiment using a totally pancreatectomized pig model of diabetes, favorable blood glucose control was observed for a week (16). These external BAP devices are suitable for use in the intensive care unit (ICU) after invasive surgery for diabetic patients. However, when subjected to a chronic illness of diabetes, it is not appropriate in terms of the patients' QOL. Therefore, it is important to develop an implant bag-type BAP. Currently, we are seeking to design and develop a subcutaneously implantable BAP device. Considering the ease of device removal, it is preferable to implant a BAP device subcutaneously. However, because subcutaneous areas lack adequate blood flow for a BAP device, it is critically essential to induce sufficient new blood vessels around the implanted device. We have therefore focused on bFGF for its strong capacity for angiogenesis. By applying a gelatinized/gelated bFGF (100 ng/ml) on the outer surface of a BAP device, the device implanted in subcutaneous tissue in the abdomen showed excellent induction of new blood vessels (32). Another attractive aspect of our designed BAP device is equipment of a port that allows injection and removal of cells at any time.

CELL SOURCES FOR BAP

Currently, researchers are actively studying on embryonic and adult stem cells as an alternative cell source for the replacement of normal human pancreatic islets. Stem cell studies have been rapidly advanced in recent years and their possibility of differentiation to insulin-secreting cells (4,8,30) has been indicated. However, the development of a method for efficiently inducing differentiation of the stem cells to pancreatic beta cells and identification of pancreatic stem cells have not yet been achieved. We have assumed that one of the reasons for such difficulties is due to multipotency and active proliferative properties of such stem cells. While studies on the utilization of porcine islets have progressed, the problem of zoonosis, biocompatibility between humans and pigs, and ethical issues has emerged. Study on transduction of an insulin gene into the body of animals or previously established cells in order to enhance insulin secretion has been conducted, but there is a risk of inducing hypoglycemia due to excessive uncontrolled insulin secretion. To address these problems, we have made great efforts to generate a tightly regulated functional human hepatic and pancreatic beta cell lines using a currently available gene transfer technology and cell culture system (22,33).

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