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Review

Our Steps toward Subcutaneous Transplantation of Macro-Encapsulated Islets

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Abstract

***Background*:** Diabetes mellitus (DM) can be cured or greatly ameliorated by adequate insulin secretion from a relatively small volume of insulin-producing cells. Cell encapsulation enables allo- and even xeno-geneic cell therapy without immunosuppression. However, recent clinical trials show that micro-encapsulated islets are not fully retrievable after transplantation. By contrast, macro-encapsulated islets can be retrieved when necessary. As to the transplantation site, subcutaneous tissue can be promising, if new strategy can overcome the hypoxic status due to hypovascularity.

In this review article, we summarized the development of macro-encapsulated islets and approaches toward subcutaneous transplantation in our laboratory over more than two decades. Our results repeatedly show that islets and encapsulated islets can be transplanted in various sites including subcutaneous tissue after pretreatment of neovascular induction. As to macro-encapsulation devices, our laboratory firstly developed mesh-reinforced poly-

vinyl alcohol (PVA) hydrogel tubes and bags; agarose-based encapsulation methods followed. After that, PVA macro-encapsulated islets were developed utilizing sol-gel transition of PVA solution through micro-crystallization, induced by freezing and thawing. Recently, we took advantage of the excellent histocompatibility of ethylene vinyl alcohol co-polymer (EVOH) to fabricate the highly porous EVOH bag. A unique macro-encapsulation device using thermo-sensitive chitosan-based gel in combination with the EVOH bag was developed. Most recently, we found that slow release of hepatocyte growth factor (HGF) from the chitosan gel can protect islets against initial hypoxic status and subsequently induce neovascularization in subcutaneous tissue to exert islet function, eliminating the necessity for neovascularization pretreatment.

***Conclusions*:** Our recent study showed that retrievable and replaceable macro-encapsulated islets can be transplanted subcutaneously without pretreatment. Although further improvements may be necessary, this immunosuppression-free approach may replace intraportal islet transplantation in the near future.

Keywords

Islet transplantation; macro-encapsulation; subcutaneous transplantation

1. Introduction

1.1 Bioartificial Organs

Bio-artificial organs that utilize living functional cells have been studied to support physiological functions of various organs when such functions are impaired. For example, utilizing living hepatocytes or hepatocyte-like cells, a bioartificial liver tries to support liver function to bridge liver failure until liver recovery or liver transplantation [1]. Similarly, a bioartificial pancreas or bioartificial islets compensate islet function utilizing living islets or islet-like tissue [2]. In bioartificial islets, islets are protected by a semi-permeable barrier that blocks immune cells or large immune-related molecules but allows the passage of small molecules such as O_2 and nutrients, including glucose and insulin. Therefore, no or much reduced immunosuppression is needed to avoid immunological resection in comparison to naked islet transplantation. It is obviously beneficial to patients to avoid immunosuppressant-related adverse events and to save costs related to immunosuppression; such costs include immunosuppressants themselves, monitoring related to immunosuppression, and additional medical costs for adverse events.

1.2 Various Types of Bioartificial Islets

Many types of bioartificial islets have been developed. The first successful bioartificial islets of encapsulation type, which used alginate-based hydrogel for islet micro-encapsulation, was published in 1980 [3]. Until then, other designs such as diffusion chambers and hollow fiber units were reported for semi-permeable barriers [4, 5].

As to micro-encapsulation, alginate-based materials were most frequently reported. In order to improve its histocompatibility or control pore size, surface modification with the polylysine-

polyethyleneimine [6], lysine/alginate [7], poly-L-ornithine-alginate [8], carboxy methylcellulose, and others [9] were used. Regarding the concern of hypoxia, hemoglobin cross-linking [10], co-encapsulation of photosynthetic oxygen generators [11], and use of CaO_2 and hemoglobin [12] were reported. In addition to alginate-based micro-encapsulation, agarose-based hydrogel was also reported [13].

In contrast to the difficulty in complete removal of micro-encapsulated islets after transplantation to the abdominal cavity or some other sites, a macro-encapsulation device that can be observed by the naked eye and treated with hands is retrievable when adverse events occur. Diffusion chambers [4] and hollow fiber units [5, 14] were used as macro-devices to encapsulate islets. In addition, macro-devices using hydrogels were also reported [15].

For an immunoisolating bioartificial pancreas, oxygen supply and biocompatibility (foreign body reaction) are two major issues, since artificial devices containing living cells are implanted without a blood supply. In addition, it is known that the intercellular structure of islets is critical to insulin secretion and β-cells do not exert their full function in a single cell fashion [16]. Therefore, insulin-producing cells should be cultured as cell clusters prior to transplantation. As to oxygen supply, model analysis of oxygen supply in cell clusters with different shapes (sphere, cylinder, and sheet) was reported [17]. To prevent central necrosis in islet grafts for subcutaneous transplantation, the theoretically largest radius was 122 μm for sphere, 100 μm for cylinder, and 71 μm in half thickness for sheet, respectively. Otherwise, macro-encapsulated islets more easily develop tissue anoxia relative to that of micro-encapsulated islets [18]. As to the O_2 supply directly to the device, a macro-device that requires daily O_2 perfusion is used in a clinical study now [19]. Concerning biocompatibility, foreign body reaction causes inflammation around the implant and tries to isolate the implant from the living organism. This mechanism usually results in fibrous capsule formation, and this membranous structure is thought to block the inward permeation of O_2 and nutrients to impair islet cell function as well as insulin outward secretion. In fact, a human clinical trial revealed that micro-encapsulated islets transplanted into an abdominal cavity was found attached to the parietal peritoneum macroscopically and surrounded by fibrous tissue microscopically [20]. These two issues are crucially important for engraftment and long-term function of encapsulated islet grafts.

1.3 Benefits of Macro-Encapsulation

As mentioned above, macro-encapsulated devices can be retrieved if necessary. Regardless of micro- or macro-encapsulation, implants should be clean and safe. However, retrievability adds a further measure of safety when adverse events occur. As to the surface area for material transfer, micro-encapsulation theoretically gives an extremely wider area in comparison to macro-encapsulation. However, micro-encapsulated devices may aggregate each other and result in much narrower practical surface areas. As to function and biocompatibility, micro-encapsulated beads need to be treated collectively and treatments are limited. On the other hand, macro-encapsulation devices can be treated individually and a wide range of adjustments, such as pore size, surface nature, and device size, are possible. In our laboratory, researchers of surgical background preferred macro-encapsulation because of its retrievability and mostly studied it from the beginning as mentioned later.

2. Pretreatment for Neovascularization at Subcutaneous Site

Subcutaneous tissue is the most easy-to-reach site in the body. However, it is well known that subcutaneous tissue is not suitable for islet transplantation due to hypovascularization [21]. To increase O_2 in the implant site, neovascularization was induced using a bFGF-releasing device before islet transplantation [22]. In this study, slow release of bFGF was secured by a gel containing 2.5% agarose and 1% hyaluronic acid in a polyethylene terephthalate (PET) mesh-reinforced PVA bag. The bFGF-impregnated device was implanted in a subcutaneous site in diabetic rats one week before islet transplantation. After one week, a richly vascularized capsule was observed around the device, and transplantation of syngeneic naked islets at the pre-vascularized sites resulted in normoglycemia until the retrieval of grafted islets 3 months after transplantation [22].

In other experiments, bFGF was incorporated in gelatin microspheres (MS/bFGF) and subsequently injected into the collagen sponge placed in a PET mesh bag. Seven days after subcutaneous implantation in diabetic rats, remarkable vascularization formed around and in the device. Islets isolated from Sprague-Dawley (SD) rats were mixed with 5% agarose for immunoisolation and transplanted into a pre-implanted bag device in diabetic Lewis rats. The recipient rats achieved normoglycemia within 2-3 days and maintained the physiological blood glucose levels for 40 days [23], suggesting that encapsulated islets can be transplanted to subcutaneous sites with the pretreatment for neovascularization. The same pretreatment for neovascularization was performed between the trapezius and rhomboid muscles of diabetic Lewis rats, and islets isolated from SD rats were macro-encapsulated in 5% agarose and transplanted. The recipients showed normoglycemia for up to 50 days after transplantation [24].

Injection of bFGF-impregnated MS/bFGF without the collagen sponge and PET bag was also shown to induce neovascularization in subcutaneous sites [25, 26]. In these studies, islets isolated from either SD rats [25] or porcine pancreases obtained from a local slaughterhouse [26] were macro-encapsulated and transplanted to subcutaneous sites pre-injected with MS/bFGF in diabetic mice. Islets were macro-encapsulated in a rod-shaped gel containing 5% agarose and 5% polystyrene sulfonic acid, and the construct was further coated with polybrene and carboxymethyl cellulose according to the study of Iwata et al. [27]. All recipients showed normalization of blood glucose levels in 5-7 days. The animals gradually gained body weight for 38-101 days in the rat islet group [25] and 24-76 days in the porcine islet group [26].

From these studies, pretreatment for neovascularization allowed subcutaneous transplantation of both naked islets and macro-encapsulated islets. Pretreatment can be achieved through diverse approaches from simple injection of MS/bFGF to implantation of bFGF-impregnating devices. However, these studies commonly used slow release of bFGF to induce neovascularization [28]. Recently, this kind of pre-treatment was found to induce not only neovascularization but also local immunotolerance for allo-transplantation of islets in rats [29]. For clinical use, further studies are needed to optimize methodologies to utilize slow release of bFGF at subcutaneous sites for transplantation of naked or encapsulated islets.

3. Macro-Encapsulation Studies in Our Laboratory

3.1 PVA Tube and Bag

Our studies on islet encapsulation started in the late 1980s as a collaborative study between the surgical laboratory of former Prof. Kazutomo Inoue and the biochemical engineering laboratory of former Prof. Yoshito Ikada. An overview of the encapsulation materials used in our studies is summarized in Table 1.

Table 1 Macro-encapsulation materials used in our experiment.

Material	Description	Merits	Demerits	References
Mesh-reinforced PVA tube/bag	Cross-linked PVA gel reinforced with mesh	High biocompatibility, in vivo stability	Difficulty in encapsulation Need of islet immobilization with gels	[30-34]
Agarose-based gel	Rod-shaped agarose-polystyrene sulfonic acid gel coated with polybrene and carboxymethyl cellulose	Used for subcutaneous xeno-Tx	Mechanical weakness Questionable in vivo durability	[22-25]
PVA gel by freezing/thawing	Mesh-reinforced PVA gel made by freezing/thawing	Storable in freezing phase	Mechanical weakness, islet damage due to freezing/thawing, foreign body reaction in long-term Tx	[35-39]
EVOH bag with chitosan gel	Thermosensitive chitosan gel encapsulated in highly porous EVOH bag	Very high biocompatibility, in vivo stability of gel enhanced by EVOH bag		[40, 41]

At the beginning, a mesh-reinforced polyvinyl alcohol (PVA) tube (MRPT) was prepared by cross-linking a 3% PVA (polymerization degree: 7200) solution with glutaraldehyde. PVA, a synthetic hydrophilic polymer, was selected due to its biocompatibility and in vivo stability. In vitro examination on permeability showed the molecular weight-dependent manner (the bigger the molecular weight, the lower the permeability rate) in which glucose, insulin, heparin, and the bovine serum albumin could diffuse while the immune globulin G was blocked. The tube was 2 mm in diameter and 40 mm in length. The thickness of the membrane was 0.2 mm. Islets (approx.

2000 in number) isolated from SD rats were encapsulated in the MRPT and transplanted to diabetic Wistar rats intra-abdominally. After transplantation, non-fasting blood glucose decreased significantly from approx. 500 mg/dL (pre-Tx) to approx. 200 mg/dL, and the effect lasted up to 97 days [30]. In this study, islets encapsulated in MRPT were free to move around, and the fusion of islets was noticed which impaired islet function. To avoid this shortage, entrapment of islets with gels in MRPT were found effective to improve insulin release in subsequent studies [31, 32].

Using a similar PVA hydrogel membrane, a mesh-reinforced PVA bag (MRPB) was also developed (Figure 1). In this device, islets tended to be trapped between the mesh fibers and could hardly move about freely. This device was used for xenotransplantation of porcine islets to diabetic rats [33]. In addition, basic fibroblast growth factor (bFGF) impregnated in gelatin microspheres and collagen-coated MRPB implanted in subcutaneous tissue could effectively induce neovascularization around the device to improve viability of encapsulated cells, suggesting that this system is suitable for subcutaneous implantation of a bioartificial pancreas [34].

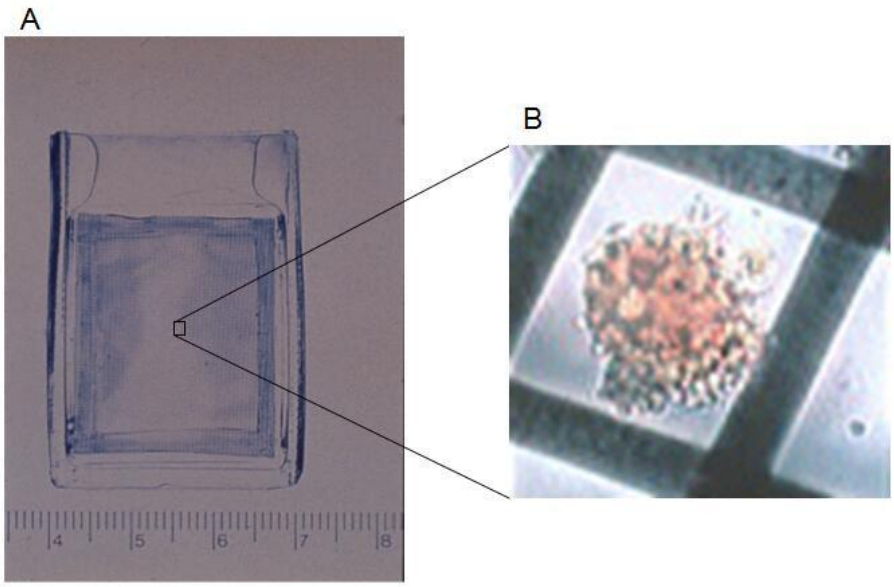

Figure 1 A: A macroscopic view of a mesh-reinforced PVA bag (MRPB). B: A microscopic view of MRPB. An islet is trapped between mesh fibers.

3.2 PVA Macro-Encapsulation

As mentioned above, PVA, a water-soluble synthetic polymer, can form a stable hydrogel with many advantages, such as a relatively lower protein-binding tendency, higher water content, and higher elasticity, as well as better biocompatibility than other synthetic hydrogels. From the early stages of our studies, the mesh-reinforcement approach was used to overcome the shortage of the weak mechanical strength of PVA hydrogel. In addition to using chemical crosslinkers, PVA hydrogel can also be prepared by freezing and thawing through micro-crystallization between PVA molecules [42]. As frequently experienced, aqueous PVA solution transits to a weak gel at low temperatures after storage in a refrigerator for a few days. Phase dissociation caused by freezing the PVA aqueous solution, in addition to low temperatures, can produce stronger gel. We utilized this unique characteristic of PVA to make PVA macro-encapsulated islets (PVA-MEIs), in which islets were embedded in a sheet-shaped PVA hydrogel (Figure 2) [35].

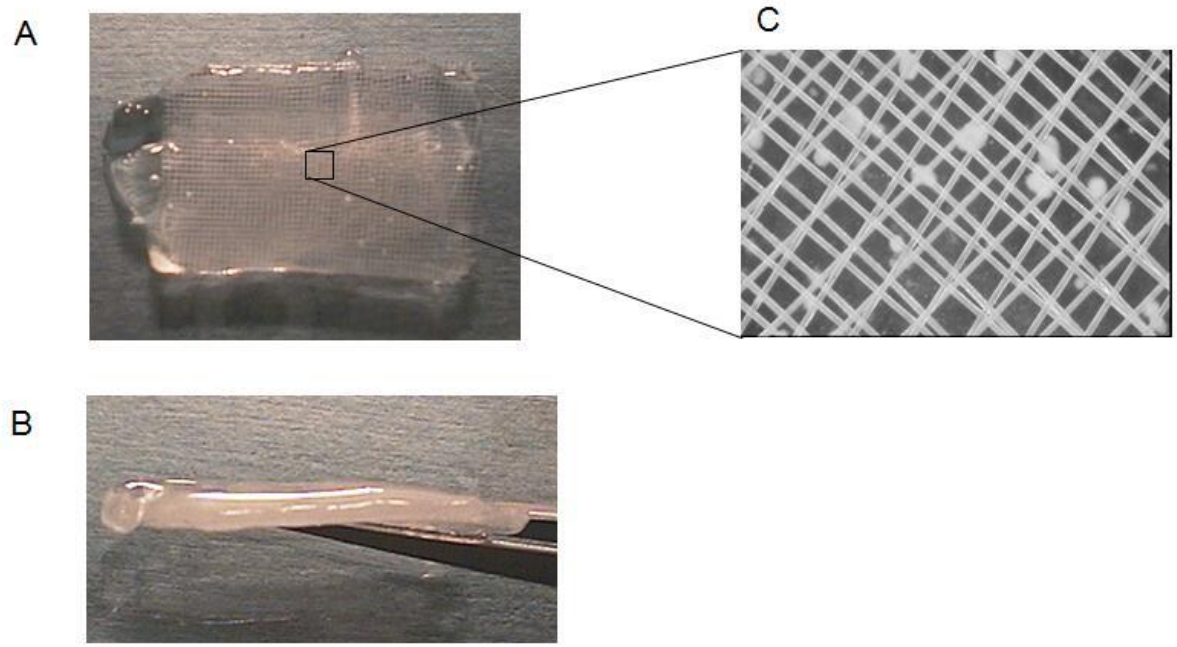

Figure 2 A: A top-down view of mesh-reinforced PVA macro-encapsulated islets (PVA MEIs). B: A side view of PVA MEIs picked by tweezers. C: A microscopic view of PVA MEIs. Islets (round-shaped things) are entrapped in PVA gel between meshes.

In the first studies using PVA-MEIs, islet function was preserved in PVA-MEIs for a longer period of time than that of naked islets in vitro. PVA-MEIs of rat islets transplanted in abdominal cavities successfully controlled hyperglycemia in diabetic mice [35]. In subsequent studies, rat PVA-MEIs transplantation remarkably alleviated diabetic renal damage in mice [36]. PVA-MEIs can be preserved for up to 30 days in the frozen phase without remarkable functional damage to embedded islets [37]. In addition, in vitro experiments to test immunoisolation showed that the addition of fresh human plasma to the culture medium did not affect the survival or function of rat PVA-MEIs. In contrast, the addition of fresh human plasma completely destroyed naked rat islets, indicating the strong immunoisolation effect of this device [38]. In a 24-week long-term observation study, islets were isolated from either Wistar or Lewis rats, embedded as PVA-MEIs, and transplanted to diabetic Lewis rats. Intraperitoneal transplantation of PVA-MEIs decreased non-fasting blood glucose levels and prevented body weight loss of diabetic Lewis rats without a significant difference between the donor strains, suggesting a protective effect against allogeneic immunity [38]. However, in this experiment, the function of transplanted devices decreased gradually in time in terms of blood glucose control (Figure 3). Although insulin-positive islets were found in the PVA-MEIs of the allo-transplantation group 24 weeks after transplantation, a dense fibrous capsule on the surface of the PVA hydrogel was noticed under histological examination, revealing that the formation of a fibrous capsule caused a decline in PVA-MEIs function (Figure 4). Management of foreign body reaction is extremely important for long-term function of encapsulated islets.

These results in PVA-MEIs were summarized in a review article [39].

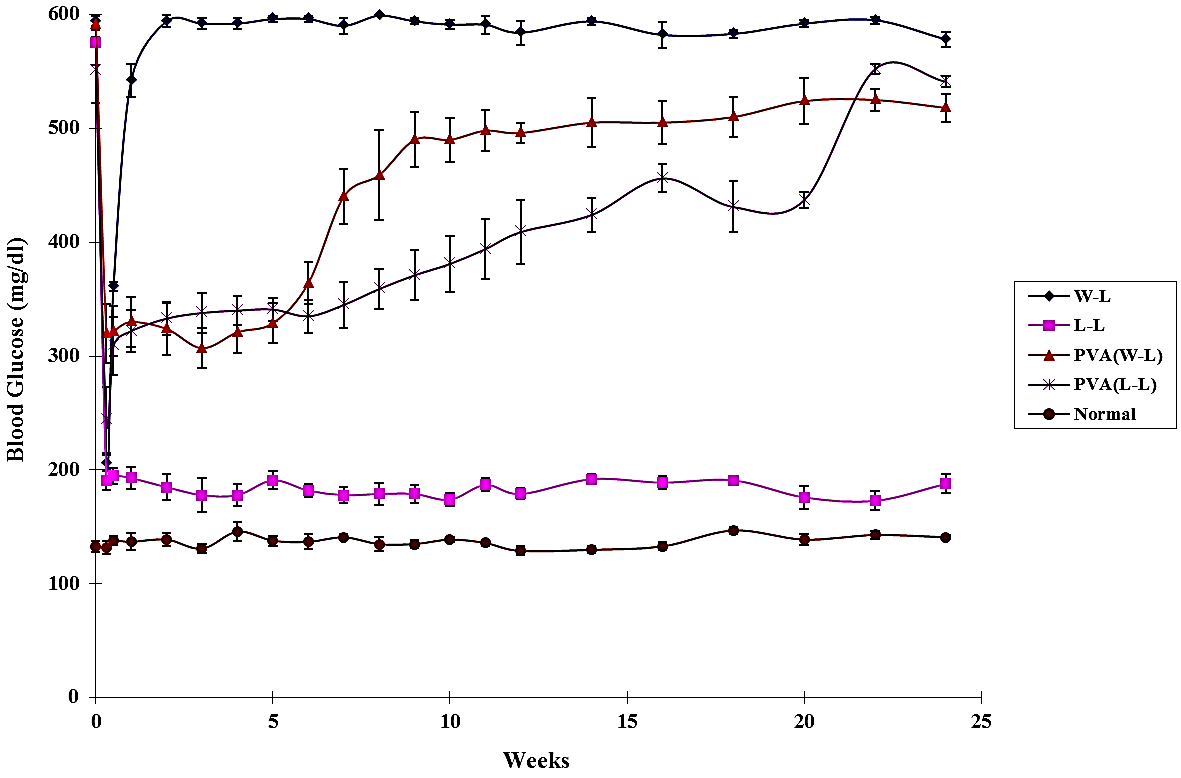

Figure 3 Non-fasting blood glucose changes in long-term (24 week) experiment. Lewis rat islets were transplanted into the renal subcapsular space of diabetic Lewis rats (L-L) and engrafted for the long term. Wister rat islets transplanted to diabetic Lewis rats (W-L) were rejected. PVA MEIs from Lewis rats (PVA(L-L)) and those from Wistar rats (PVA(W-L)) showed similar changes between L-L and W-L. However, the effects were gradually decreased over time.

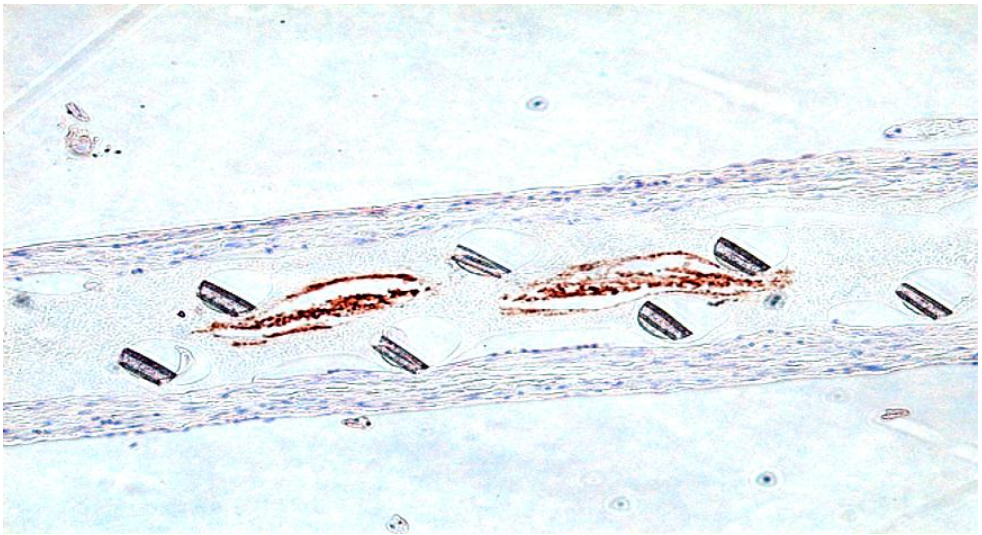

Figure 4 Microscopic view of PVA MEIs of PVA(W-L) group after immunological staining for insulin. Insulin-positive islets were observed between mesh fibers. However, flat but dense fibrous membrane formed on the PVA gel.

3.3 EVOH bag

Based on the lessons learned from studies on PVA-MEIs, we tried to develop a more biocompatible device for encapsulation. Ethylene vinyl alcohol co-polymer (EVOH) is known to be highly biocompatible, and hemodialysis using an EVOH membrane proved excellent biocompatibility [43]. Thus, we decided to use an EVOH membrane as an envelope for macro-encapsulation. EVOH membranes are also well known as gas barriers for food packaging; therefore, a highly porous EVOH membrane was fabricated and provided by Kuraray Co., Ltd., a major chemical company in Japan, for our collaborative study.

In the beginning, the highly porous EVOH membrane and a separate port part which includes a tube for injection and a part to connect the tube and bag were custom made by injection molding using the same EVOH resin provided by Kuraray. Two pieces of EVOH membranes were heat-sealed with the injection port to fabricate a highly porous EVOH bag device.

For immunoisolation, a thermosensitive chitosan-based gel was selected. This is an aqueous solution of chitosan (2.5%) dissolved in 0.1M acetic acid and titrated with β-glycerol 2-phosphate disodium salt hydrate (0.8 W/V) with a pH of 7.4 at room temperature. The chitosan-based solution undergoes sol-gel transition in a few minutes when the environmental temperature rises to 35 degrees Celsius. Thus, temperature-dependent gel formation, an islet-friendly method, needs nothing but the increase of environmental temperature to body temperature (Figure 5). Our previous studies showed that chitosan gel can protect β-cells against inflammatory cytokines; we used it in rat to mouse xenotransplantation [44, 45].

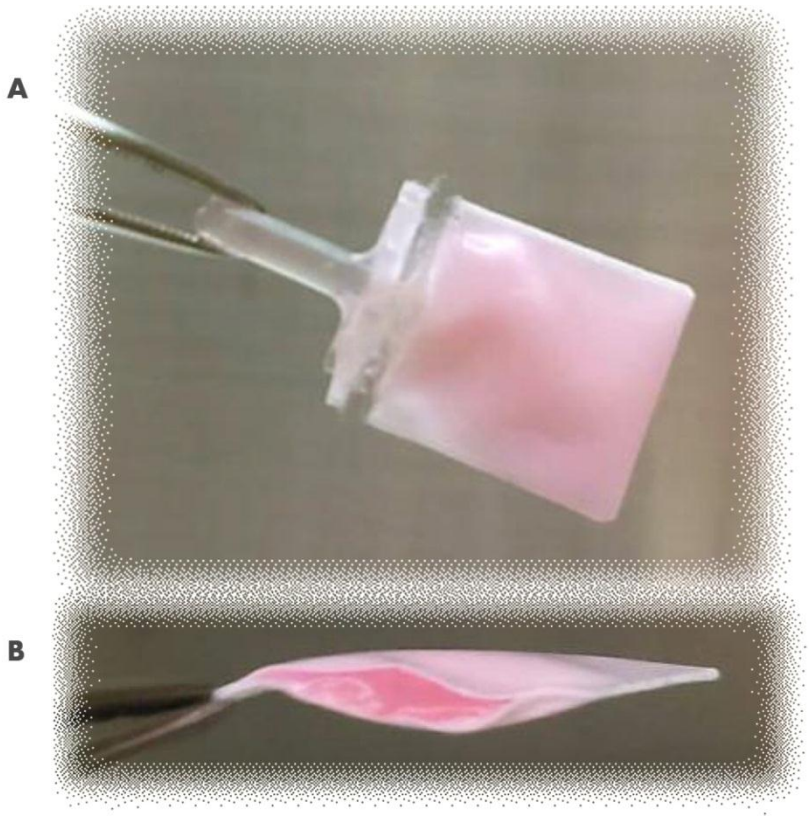

Figure 5 A: A macroscopic view of an EVOH bag filled with chitosan gel. B: A cross-sectional view of an EVOH bag filled with chitosan gel.

In vitro examination on chitosan gel-EVOH bags showed that islets maintained good viability both in chitosan gel alone and in chitosan gel-EVOH bags with minimal apoptosis for at least 5 days, while central necrosis and many apoptotic cells were found in naked islets. Glucose-responsive insulin release was also sustained in both chitosan gel alone and EVOH groups for up to 7 days, whereas in the naked islet group, islets were unable to secrete insulin after a 5-day culture, suggesting that islets embedded in chitosan gel preserved the capacity for insulin secretion even when enclosed in the EVOH bag. Insulin release in the culture condition continued at least for 30 days in the chitosan gel-EVOH bag group, whereas islets embedded in the chitosan gel alone group lost insulin production by 20 days. This seemed to reflect our observation that chitosan gel continuously degraded in PBS while the weight loss of chitosan gel in EVOH bag was remarkably inhibited [40]. It is thought that the EVOH bag extended the function of gel embedded islets.

In an in vivo experiment, rat islets (650-800 IEQ) were macro-encapsulated in chitosan gel-EVOH bags and transplanted into the abdominal cavities of diabetic mice. The transplanted mice exhibited lower blood glucose levels and regained body weight during a 4-week observation period (Figure 6). They also had higher levels of serum insulin and C-peptide, with an improved blood glucose disappearance rate, measured by an intra-peritoneal glucose tolerance test at the end of the observation period. Retrieved macro-encapsulated islets had minor tissue adhesion, and histology showed a limited number of mononuclear cells and fibroblasts surrounding the implants. In addition, most of these cells accumulated near the port part, suggesting that the port part of the device was less biocompatible than the EVOH membrane due to some problems in the molding process. Furthermore, no invasion of host cells into the EVOH bags was noticed, and the encapsulated islets were intact and positive for insulin and glucagon by immune-staining [40].

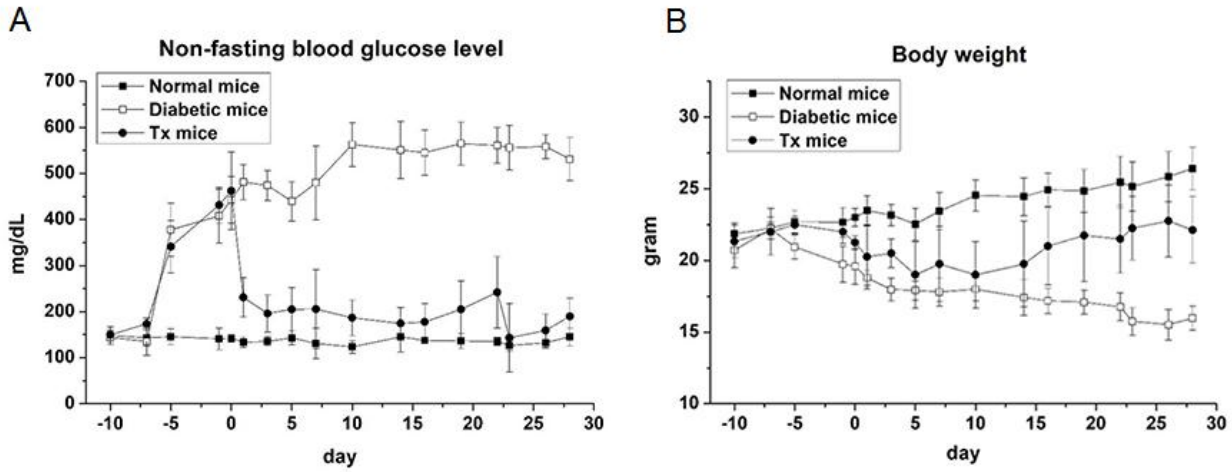

Figure 6 A: Transplantation of the macro-encapsulated rat islets in chitosan gel-EVOH bags decreased blood levels of diabetic mice. B: The mice received an implant also regained body weight gradually.

More recently, we tested subcutaneous transplantation of these EVOH-macro-encapsulated islets with bFGF [41]. In this study, macro-encapsulated rat islets were transplanted at subcutaneous sites that were pretreated with a bFGF-impregnated collagen sponge for neovascularization (2-time operation group). In another group, bFGF was added to the chitosan gel in EVOH bags and transplanted to subcutaneous sites without pretreatment (1-time operation

group). Between the 2-time and 1-time operation groups, the former showed a decrease in non-fasting blood glucose levels and relatively higher serum insulin levels with improved renal and metabolic biomarkers. On the other hand, the 1-time operation group showed no transplantation effects in comparison to diabetic control animals [41]. We concluded that bFGF was only effective when used for pretreatment of neovascularization at the subcutaneous site.

Now, we are trying hepatocyte growth factor (HGF) to enable 1-time (without pretreatment) subcutaneous transplantation of macro-encapsulated islets. We found, in a preliminary experiment, that slow release of HGF from chitosan gel can protect islets against initial hypoxic status and subsequently induce neovascularization in subcutaneous tissue to exert islet function, eliminating the necessity for neovascularization pretreatment. The details of this study will be presented elsewhere.

3. Discussion

As described above, hydrogels such as PVA membrane and gel, agarose gel, and chitosan gel have an immunoisolation effect that can be used for rat to mouse xenotransplantation without immunosuppression. The stability of the hydrogel seems to determine the duration of the immunoisolation effect. For example, biologically stable PVA hydrogel can protect islets up to 24 weeks. On the other hand, agarose gel and chitosan-based gel in which no physiochemical bonds are formed between molecules, did not show such a long effect of immunoisolation. A possible exception might be chitosan gel in EVOH bags in which EVOH bags continuously inhibit the leakage of chitosan molecules, maintaining the gel weight for a longer time in vitro, and thus presumably the immunoisolation effect in vivo. We are now trying to enhance the stability of chitosan-based gel and testing the long-term effect of immunoisolation in EVOH-macro-encapsulated islets.

The biocompatibility of the device seems very important for the encapsulated islets to exert long-term function. Tuch et al. [20] reported thick fibrous tissue around intraperitoneally transplanted micro-encapsulated human islets 16 months after transplantation [20]. On the other hand, Yang et al. [46] reported that chitosan-coating improved the biocompatibility of alginate-encapsulated islets, enabling long-term function of intraperitoneally transplanted micro-encapsulated allogeneic islets [46]. Since EVOH has excellent biocompatibility, our EVOH bag causes minimal foreign body reactions and EVOH-enveloped macro-encapsulated islets are expected to exert their function for a long period of time.

Hypoxia is another critical issue that limits islet survival. Even though islets may survive under low oxygen tension, oxygen availability influences islet function dramatically. In fact, Safley et al. [47] intraperitoneally transplanted micro-encapsulated adult porcine islets into diabetic non-human primates. They found that plasma levels of porcine C-peptide decreased over time. Histology of explanted islet capsules showed scant evidence of a host cellular response, and viable islets could be found. Central necrosis was noticed in many of the encapsulated islets after graft failure, and explanted islets expressed endogenous markers of hypoxia (HIF-1α, osteopontin, and GLUT-1), suggesting a role for non-immunologic factors, likely hypoxia, in implant failure. They concluded that new approaches to prevent hypoxic damage are necessary to achieve long-term function of micro-encapsulated islets [47].

As for commercial products, macro-encapsulation devices are developed by TheraCyte™, ViaCyte, and Cell Pouch™, and are currently undergoing clinical trials. The TheraCyte™ implant

system is a polymeric chamber which is fabricated from dual-layer polytetrafluoroethylene (PTFE) membranes with an outer layer of woven polyester mesh [48]. The inner PTFE membrane can protect embedded allogenic islets from rejection by the recipient while the outer polyester mesh can promote neovascularization when implanted subcutaneously. ViaCyte Encaptra, a similar product to TheraCyte™, uses human embryonic stem cell-derived pancreatic precursor cells as a cell source. However, the second generation Encaptra, PEC-Direct™, is a non-immunoprotective implant. In order to enhance the oxygen availability in macro-encapsulated islets, the Sernova Cell Pouch System™, another subcutaneously implantable device, is specifically designed to be non-immunoisolating to promote pre-vascularization [49]. Application of an immunosuppression regimen on the recipient is required to avoid transplant rejection for the above devices and thus shall compromise long-term function of the devices.

Regarding the scalability of the macroencapsulation device, an increasing volume of devices as well as an increasing number of embedded islets may cause substantial differences in oxygen-nutrient gradients within the device. Likewise, an increase in device size can also cause nonhomogeneous distribution of islets within the device. Therefore, implantation of multiple small devices shall be superior to a single large device for clinical practice. In addition, it is known that islets secrete paracrine signals to regulate insulin secretion to neighboring islets. Apparently, the islet density is critical since this factor determines how many islets can be loaded within one device and subsequently determines the number of devices needed for clinical application. However, the optimal islet density varies with the design/materials of the device. As mentioned above, pretreatment for neovascularization of the transplantation site is one possible approach. In addition, engraftment may be improved by using some material to protect islet cells against hypoxic conditions while the same or other material induces neovascularization to increase the partial pressure of oxygen. We are now trying to realize this approach to avoid pretreatment and simplify the transplantation procedure.

4. Conclusions

The importance of oxygen supply and biocompatibility of material for macro-encapsulated islets was introduced and discussed based on our laboratory's studies. With advances in encapsulation technology, subcutaneous transplantation of macro-encapsulated islets may be an option for the treatment of type 1 diabetes with unstable glycemic control in the near future.

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Author Contributions

SS and KCY wrote this article. SYY and PC provided experimental and literature data.

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Competing Interests

The authors have declared that no competing interests exist.

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