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Current status of encapsulated islet transplantation

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ABSTRACT

Islet transplantation is a treatment modality for diabetes mellitus that can maintain insulin levels within a physiologically appropriate range. However, wider clinical application is limited by insufficient donor numbers and a need for lifelong immunosuppression. Despite various clinical and preclinical trials, there is no single standard immunosuppressive regimen that can suppress acute and chronic immune reactions with lower toxicity to grafted islets. One of the strategies for overcoming lifelong immunosuppression is the incorporation of encapsulation technology, which can provide a physical immune barrier by keeping out high molecular weight immune system components, while still allowing low molecular weight oxygen, insulin and nutrients to pass through. Encapsulated islet transplantation approaches that have been studied so far include macroencapsulation, microencapsulation, conformal coating and nanoencapsulation. Herein we will review the basic concepts of islet encapsulation technique, earlier works to recent progress related to clinical studies and corporate investigations on encapsulated islet transplantation.

1. Introduction

Islet transplantation is a treatment modality for diabetes mellitus that can maintain insulin levels within a physiologically appropriate range. After a landmark study that adopted the Edmonton Protocol was published in 2000 (Shapiro, Lakey, Ryan, et al., 2000), many centers have reported promising results in human islet transplantation with immunosuppressive regimens including daclizumab, low dose of sirolimus and tacrolimus (Shapiro, Ricordi, Hering, et al., 2006). The Collaborative Islet Transplant Registry reported islet graft survival (C-peptide ≥0.3 ng/mL) rates of 92% at 1 year and 83% at 3 years during the period 2007–2010, and in later years, 44% insulin independence at 3 years after transplantation (Barton, Rickels, Alejandro, et al., 2012). The disadvantages of the current approach to islet transplantation are the need for at least two donor pancreases for most recipients and graft failure, which occurs within a relatively short period of time compared with whole pancreas transplantation (Frank, Deng, Huang, et al., 2004). Poor vascularization and relative hypoxia of the transplanted cells, continuing destruction by autoimmunity and allograft rejection (Blondet, Carlson, Kobayashi, et al., 2007) are also all thought to contribute to early graft failure. Furthermore, subsequent studies reported that rapamycin and tacrolimus *per se* may have deleterious effects on islets of rats and humans (Vincenti, Friman, Scheuermann, et al., 2007). Several new immunosuppressive agents have been introduced including agents that deplete T cells (hOKT3r [Ala-Ala], thymoglobulin and alemtuzumab), and B cells (rituximab) or induce peripheral tolerance (anti-CD40L antibodies and LEA29Y [belatacept]). Despite various clinical and preclinical trials, there is no single standard immunosuppressive regimen that can suppress acute and chronic immune reactions while being less toxic to grafted islets.

One of the strategies for overcoming lifelong immunosuppression is the incorporation of encapsulation technology. Micro- and macroencapsulation are immune isolation systems that can keep out high molecular weight immune system components such as immune cells (7 μm) and antibodies (~150–900 kDa), while allowing low molecular weight oxygen, insulin (~6 kDa), nutrients and hormones to pass through (Dufrane & Gianello, 2012). Therefore, encapsulation technique would prevent allograft and autoimmune rejection, although it will not completely protect against chemokines and cytokines with lower molecular weights.

2. Structural approaches for encapsulation of islets

Methods for the encapsulation of pancreatic islets can be categorized into four groups: 1) macroencapsulation which encapsulates large number of islets within a given device; 2) microencapsulation of one to a few islets within spherically shaped permselective capsules; 3) conformal coatings that cover individual islets; and 4) nanoencapsulation or layer-by-layer coating.

Conflict of interest: All authors declare that there is no conflict of interest associated with this manuscript.

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2.1. Macroencapsulation

Macrocapsules contain a large mass of islets within a given device and are divided into two main types: intravascular and extravascular. An intravascular macrocapsule is directly connected to the host artery and vein, allowing blood flow into the hollow fibers (Monaco, Maki, Ozato, et al., 1991). Islets are placed near the fibers and receive oxygen and nutrient supply directly from the blood flow, while protected from immune cells by the fiber membrane. However, intravascular macrocapsules have had severe problems with embolization and formation of blood clots. Several investigators have introduced intravascular devices and proved long-term islet function after xenogeneic transplantation in a canine model of diabetes without immunosuppression (Sullivan, Maki, Carretta, et al., 1992). However, the US Food and Drug Administration (FDA) could not approve this hybrid artificial pancreas for clinical trials because a long-term followed-up dog abruptly died owing to breakdown of the carotid artery device connections (Scharp & Marchetti, 2014).

Extravascular macrocapsules have been tested in many shapes including rod, tube or sheet. An attractive aspect of macroencapsulation is that it may be retrieved or reloaded. Also macrocapsules have greater mechanical strength than microcapsules. However, one of the potential disadvantages is the limitation of oxygen diffusion and nutrient transport. Also, the packing density and surface area-to-graft tissue would be critical for clinical application.

In 1980, Valente, Ferro, Campisi, Parodi, and Tosatti (1980) implanted human islets encapsulated within extravascular macroencapsulation chambers into 13 patients with diabetes, and two patients subsequently transiently stopped insulin therapy. After successful results with a rodent model in 1991 (Lacy, Hegre, Gerasimidi-Vazeou, Gentile, & Dionne, 1991), Scharp, Swanson, Olack, et al. (1994) conducted a clinical study, which was approved as an investigational new drug (IND) by the US FDA (BB-IND 5103). Subcutaneous implantation of 150–200 islet equivalents (IEQs) of human islets encapsulated in acrylic-copolymer hollow fibers was performed in patients with type 1 and type 2 diabetes and normal control subjects. Two weeks after the implantation, capsules were explanted and showed minimal implant site attachment and viable islets within the device. The retrieved, encapsulated islets from type 1 and type 2 diabetes patients did not respond to glucose stimulation alone, while this response was present in encapsulated islets from the normal control subjects. The authors discussed that hyperglycemia in subjects with diabetes would have caused the impairment of glucose stimulated insulin secretion.

In the 1990s, Baxter Healthcare (Deerfield, IL, USA) developed a planar device of two composite membranes and a loading port. This macrocapsule, which was later named as the TheraCyte® Implant System, was 4 cm in length, shaped like a teabag and made of bilayered polytetrafluoroethylene membrane. Studies in a rodent model supported its biocompatibility (Rafael, Wernerson, Arner, Wu, & Tibell, 1999). Transplantation of neonatal pig islets using the TheraCyte device reversed diabetes for up to 16 weeks in diabetic mice, and graft islets survived up to 8 weeks in nondiabetic cynomolgus monkeys with no evidence of reaction with adjacent subcutaneous tissue (Elliott, Escobar, Calafiore, et al., 2005). Since the original patent has lapsed, several different groups including Betalogics of Janssen Pharmaceuticals and ViaCyte, as well as other academic investigators, are performing further investigations and testing different modifications in an attempt to create a clinically relevant device (Scharp & Marchetti, 2014). One of the aims of these modifications is to make an encapsulation device for human embryonic stem cell-derived islet tissue. With embryonic stem cell grafts, there may be the possibility of undifferentiated stem cells or teratoma formation within the graft tissue. The macroencapsulation device has an advantage in keeping the graft cells from escaping from the device. Moreover, some grafts would contain dilated ducts and or cysts derived from these ducts that could potentially impinge upon surrounding tissue. Implantation within a durable macroencapsulation device could constrain such structures, and offer an additional level of safety by enabling easier retrieval of the implanted cells (Schulz, Young, Agulnick, et al., 2012). ViaCyte is currently in clinical trials using human embryonic stem cells encapsulated in a macrodevice, which is further discussed in the later part of this review.

Islet Sheet is also a planar flat sheet device, the production of which began in the late 1990s. After implantation of six Islet Sheets containing 75,000 IEQs into the omentum of a pancreatectomized beagle, euglycemia was maintained for 84 days (Storrs, Dorian, King, Lakey, & Rilo, 2001). Later, human islets were encapsulated within Islet Sheet and transplanted into the subcutaneous space of rats, with demonstrated islet survival after explantation (Lamb, Storrs, Li, et al., 2011). Recently in 2014, Krishnan, Arora, Alexander, et al. (2014) evaluated the host vascular response to xenogeneic islets encapsulated within the Islet Sheet device. The dorsal window chamber model was surgically constructed out of a segment of dorsal skin between two titanium frames (Moy, White, Indrawan, et al., 2011). The skin on one side of the window was excised and the window was then covered using a circular glass slide, allowing the subdermal microvasculature of the opposing skin to be visualized. Laser speckle imaging and wide-field functional imaging were used to monitor the microvascular environment. After transplantation of Islet Sheet devices, significant changes in blood flow, hemoglobin oxygen saturation and vascular density were noted within the first 2 weeks.

Beta-O_2 Technologies Ltd. developed an oxygen-refueled macrochamber (β Air) that is composed of two compartments: islets immobilized in an immune protected compartment and an O_2 supply compartment (Ludwig, Zimerman, Steffen, et al., 2010). A high concentration of O_2 (60%) can be injected daily through a subcutaneous port, which slowly diffuses to the islet immobilized compartment. With successful data in rodents (Ludwig, Rotem, Schmid, et al., 2012) and pigs (Neufeld, Ludwig, Barkai, et al., 2013), investigators have implanted β Air in a 63-year-old patient with type 1 diabetes and followed for 10 months without immunosuppressant (Ludwig, Reichel, Steffen, et al., 2013). Persistent graft function with regulated insulin secretion and preservation of islet morphology was demonstrated. Currently, a clinical trial using β Air is recruiting patients in Sweden (Table 1).

A monolayer configuration of macroencapsulated pig islets was introduced in 2010 by Dufrane, Goebbels, and Gianello (2010). Subcutaneous implantation of this monolayer cellular device significantly improved hyperglycemia (HbA1c <7%) in primates for 6 months without immunosuppression. In this system, islets were seeded as a monolayer on an acellular collagen matrix, enhancing their interaction with a biologic membrane and increasing islet concentration per unit surface area (Dufrane & Gianello, 2012). A phase I clinical study to assess the safety and efficacy of encapsulated human islets in a monolayer cellular device was registered in Belgium, but has not been updated since 2011 (Table 1).

In 2004, Qi, Gu, Sakata, et al. (2004) introduced a sheet-type macroencapsulation device using polyvinyl alcohol (PVA) hydrogel, which was prepared by freezing and thawing method. Xenogeneic transplantation using this hydrogel sheet was effective in lowering blood glucose level in rodents. Sakata, Gu, Qi, et al. (2006) demonstrated that xenogeneic islet transplantation using PVA-based bioartificial pancreas improved glycemic status and renal dysfunction in rodents. In 2010, Qi, Shen, Yanai, et al. (2010) tested the usefulness of PVA macroencapsulation method in long-term (up to 30 days) cryopreservation of graft islet. This group also observed insulin-positive islets at 24 weeks after allogeneic transplantation in rodents (Qi, Yamamoto, Imori, et al., 2012). Although this device has not reached clinical trial so far, it has unique characteristics and potential usefulness in cryopreservation of graft islets.

2.2. Microencapsulation

Microencapsulated islets are microcapsules containing one to a few islets. The spherical configuration of these microcapsules results in a higher surface-to-volume ratio than does the tube or disk