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Chapter 11

Avoiding Immunosuppression for Islet Transplantation: Use of Protective Biomaterials

Michael Alexander, Huy Nguyen, Antonio Flores, Shiri Li, Paul De Vos, Elliot Botvinick and Jonathan Lakey

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Abstract

Islet transplantation, with the advent of the Edmonton protocol in 2000, has offered a significant alternative for long-lasting treatment of type 1 diabetes. However, the immunosuppression required for transplantation has the cytotoxic effect on pancreatic islets, and thus limiting the long-term efficacy of the transplant. Immediate loss of islets after transplant was also observed because of immediate blood-mediated inflammatory response (IBMIR), which kills islets transplanted in the liver through portal vein. There is also commonly a lack of microvascular blood supply to the transplanted islets. In this chapter, we will review the variety of technologies used to protect transplanted islets against toxicity of immunosuppression, immune rejection, and inflammatory response. We will evaluate the mechanisms of these technologies and their progress in solving the challenges to islet transplantation. The technologies include encapsulation of transplanted islets in various polymers, transplants in sites other than the liver, and creation of new prevascularized transplant site. These technologies offer several mechanisms to prevent immune rejection or immediate contact with cytotoxic inflammatory response, in addition to maintaining islet integrity. New transplant sites are also being developed to support the islets, by allowing establishment of microvasculature and innervation, prior to addition of the islets.

Keywords: cell encapsulation, type 1 diabetes, islet transplants, microcapsules, cell engineering

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1. Introduction

Over 25 million people in the United States (USA) suffer from diabetes, with approximately 5% characterized as type 1 diabetes (T1DM). Diabetes is ranked as the seventh leading cause of death in the USA. T1DM is characterized by the autoimmune-mediated destruction of the β-cells of the pancreas, resulting in insulin deficiency [1]. The current method of treatment for T1DM is insulin injection to maintain blood glucose control, which treats the symptoms but not the underlying disease.

With the invention of the Edmonton protocol in 2000, islet transplantation has become an attractive treatment for T1DM. As a treatment option, islet transplantation meets the goal of treating the disease rather than the symptoms. The end goal of islet transplantation in patients is the elimination of exogenous insulin dependence, allowing for those with T1DM to return to normal lives without constant monitoring of their blood glucose levels. There have been a total of 677 islet transplant recipients from 2000 to 2010. The success of the treatment has improved as well, where 27% of recipients achieved 3 years of insulin independence before 2007. After 2007 that rate has increased to 44%. Compared to insulin injection regimen, islet transplantation resulted in significant reduction in episodes of hypoglycemia unawareness [2].

Islet transplantation faces two challenges from the host immune system: the rejection of the transplanted islets as foreign body and the existing autoimmunity against β-cells. Immunosuppressive drugs such as sirolimus and rapamycin used in the Edmonton protocol has toxic side effects on islets [3, 4]. As such, there is an impetus to move away from the use of immunosuppressive therapy and instead shift toward developing physical barriers against transplant rejection and autoimmunity.

Cell encapsulation to provide physical barrier has been tested in treating other diseases such as neurodegenerative diseases, pain, and epilepsy to name a few. So far, encapsulation has been used primarily to treat T1DM [5–9]. By providing a physical barrier to immune rejection, islet encapsulation has been shown to allow transplanted islet to function normally and avoid the use of immunosuppression [10, 11].

2. History of animal and human trials of islet encapsulation

The first encapsulated islet transplants occurred in 1980, where islets in an alginate hydrogel transplanted intraperitoneally into diabetic rats achieved normoglycemia for 3 weeks, compared to 8 weeks for nonencapsulated islets [12]. Currently, there are a number of achievements in encapsulating islets seen in small and large animal studies, as well as in early phase clinical trials. A syngeneic transplant of nonobese diabetic (NOD) into prediabetic islets diabetic NOD recipients, using 5% agarose encapsulating 1500–2000 islet equivalents (IEq), showed that intraperitoneal implantation as well as omental pouch transplants demonstrated prolonged euglycemia for a period of 100 days compared to 8 days for unencapsulated islet transplants [13]. This study was repeated in 2006, where the same period of normoglycemia was observed in transplant recipients. In addition, when the devices were removed after 400 days, viable

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islets were recovered with a small percentage of necrotic cells [14]. Aside from agarose, polyethylene glycol-poly lactic-co-glycolic acid (PEG-PLGA) has been used to encapsulate 500–600 IEq islets for syngeneic transplant into streptozotocin (STZ) induced diabetic BALB/c mice, where over half of the recipients achieved normal glucose levels for up to 100 days [15].

Results in large animal studies have mostly mirrored that of the small animal trials. Diabetic canine recipients, receiving 15,000–20,000 IEq islets/kg in alginate microcapsule into the intraperitoneal cavity, were able to maintain normoglycemia without insulin injection for up to 110 days, with c-peptide detectable in the blood for more than 1 year [16]. In 2010, allogeneic transplant in nonhuman primate was tested using subcutaneous and kidney capsule transplants of alginate micro and macroencapsulated islets, at a dose of 30,000 IEQ/kg. In this study, normoglycemia was observed for 28 weeks [17]. In a xenotransplant study of neonatal porcine islets into diabetic cynomolgus monkey, 10,000 IEq/kg of alginate encapsulated islets resulted in more than 40% reduction in injectable insulin dose compared to preimplantation [18].

The first human clinical trial of encapsulated islets transplant in T1DM was reported in 1994. In a type 1 diabetes patient, a postoperative kidney transplant maintained on low dose immunosuppression initially received 10,000 IEQ/kg of cadaver human islets encapsulated in an alginate microcapsule followed by a repeat infusion of 5000 IEQ/kg 6 months later. The patient's insulin requirements were reduced to 1–2 insulin units per day, and eventually he was able to discontinue all exogenous insulin after 9 months [19]. In 2006, human cadaveric islets (400,000–600,000 IEQ) were encapsulated into sodium alginate beads and placed intraperitoneally into two diabetic patients. The patients showed improved daily glucose levels and a decline in daily exogenous insulin intake. However, neither patient became insulin independent [20].

Living Cell Technologies Ltd. an Australia company has achieved the best outcomes for encapsulated islet transplants. The company, which owns a pathogen-free pig farm in New Zealand, performed xenotransplantation of alginate encapsulated fetal pig islets in several human clinical trials. The most significant achievement has been in the reduction of hypoglycemic episodes to around 40%. Several patients achieved improvements in daily glucose levels and a reduction in exogenous insulin dosing, while two patients became insulin independent after 4 months [21, 22].

Unfortunately, there is a lack of consistency in the human clinical results. For example, a human clinical trial by Tuch et al. used alginate encapsulated human islets and tracked the presence of plasma C-peptide levels for up to 2.5 years, ultimately resulting in no change in insulin requirements for the recipients [23]. While these early phase clinical trials aim to ensure safety and determine optimal islet dose, most of the trial patients do not achieve sustainable insulin independence.

3. Biomaterials used for islet encapsulation

One of the important steps to bring islet encapsulation into widespread clinical use is to develop a standard for the type of biomaterial used and the dose of islets to be infused.

The type of biomaterial has also been shown to affect graft survival. A test of several encapsulation methods using alginate with or without poly L-lysine (PLL) as well as with high guluronic (G) or mannuronic (M) acid in mouse recipients showed that significant results were achieved with PLL-free high M microcapsules, showing sustained normoglycemia for 8 weeks [24]. Likewise, improved capsule integrity and graft function could be achieved by altering the concentration of alginate in their xenotransplants into diabetic Lewis rats [25].

Currently, the most common employed method for islet encapsulation involves alginate microcapsules [24, 26, 27]. The original device was developed over three decades ago as capillary fibers in a culture-coated medium [28], shaped as arterial-venous shunts into diabetic canines. These devices showed promising results with several canines achieving reduced insulin requirements [29, 30]. Vascular shunts are limited by the volume and number of islets that can be contained within the fibers. Elongation of the fibers resulted in increased fibrosis, leading to abandonment of this device as the higher dose of islets needed for human recipients would require such large fibers that resulted in a large amount of fibrosis [31]. Other macroscale devices have seen less use due to their increased immunogenicity as well as the larger diffusion parameters required for oxygen and nutrients to reach the cell.

Nanoencapsulation has an advantage compared to other techniques because of its more efficient diffusion capability. With a better surface area to volume ratio, this means that nanoencapsulation can improve insulin response time to blood glucose levels, offering the protection of encapsulation without compromising tissue function due to the physical barrier. PEG has been used for nanoencapsulation devices and can be cross-linked through exposure to UV or visible light. This characteristic also allows for a reduction in the amount of damage done to the capsule's inner cells normally achieved by other cross-linking methods. On the other hand, PEG biocompatibility still leaves much to be desired compared to other hydrogels, and complete protection from cytokines is still not achieved [32]. Despite these concerns, some success has been attained with these gels [33].

By far the most common encapsulation device is a microscale vehicle. These capsules have mechanical stability, optimal surface area to volume ratio, and have enhanced immunologic profiles [26, 33]. Microscale device is also easily made using standard droplet-based encapsulators that produces consistent size and shape of the resulting capsules [34, 35], as shown in **Figure 1**.

Microcapsules can also be easily made using materials other than alginate. The most common synthetic chemicals used for microcapsule production are poly ethylene oxide, poly acrylic acid, poly vinyl alcohol, polyphosphazene, and polypeptides and their derivatives. Natural occurring hydrogels include gelatin, fibrin, agarose, hyaluronate, chitosan, and alginate [36, 37]. Poly glycolic and lactic acid polymers continue to be the most commonly used synthetic materials used in medical devices.

Regardless of the materials used, capsule materials still face the fundamental flaw of being foreign materials. Thus there will always be the possibility they will elicit a greater immune response, eventually leading to fibrosis and loss of the encased cells. As such, it is important to ensure that the materials are nontoxic and purified prior to microcapsule production.

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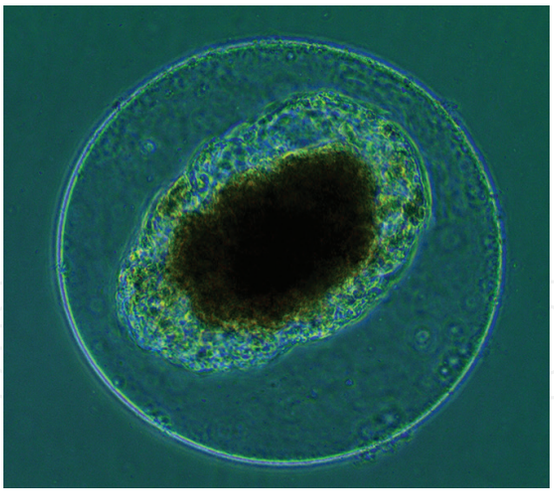


Figure 1. Porcine islet encapsulated in alginate. Isolated juvenile porcine islets (from 22 to 24 days old pigs, matured for 7 days) were encapsulated in 2.5% low viscosity mannuronate (Pro-Nova UPLVM) alginate (Novamatrix) using an electrostatic gas-driven encapsulator (Nisco Engineering AG).

Because of their tolerability, biologically derived materials have been of interest for islet encapsulation. One possible material is collagen, a naturally derived polymer that is the most widely used in medical devices today. However, collagen gels exhibit poor strength, which are expensive and have high variability of purity, making standardization of the process a problem [37]. Comparatively, alginate has excellent biocompatibility, hydrophilic properties, easy gelation process, stable architecture, and relatively low cost. Alginate is polysaccharide derived from seaweed, which can be highly purified to prevent foreign body response [38]. Impure alginate has been implicated in islet cell necrosis and recruitment of inflammatory mediators [39].

Alginate is a polymer of 1-4 linked β-D-mannuronic acid (M) and 1-4 linked α-L-guluronic acid (G). This polysaccharide can contain varying concentrations of M and G carbohydrates, which provides a variety of molecular weight, stability, permeability, and immunogenicity. High G alginates form gels, which are smaller and stronger than high M alginates [38]. High-M alginate was often avoided when immunosuppression was the desired outcome, because mannuronic acid tends to provoke both innate and antibody-mediated immune response, independent of the type of cation used for cross-linking (Ca^{2+} or Ba^{2+}). High-M also triggers macrophages to secrete pro-inflammatory cytokines including IL-1, IL-6, and TNF-α through interactions with the monocyte CD14 receptor [39]. However, recent studies seem to contradict these earlier findings, reporting a higher amount of cellular adhesion to high-G alginate capsules when compared to high-M alginate [40, 41]. It is likely that the observed difference in the immune response depends not on the identity of the alginate material, but instead on the quality of the alginate purification method [42, 43].

Using surface modification, poly-methyl co-guanidine-cellulose sulfate/poly l-lysine-sodium alginate (PMCG)-CS/PLL was used for syngeneic transplant into T1DM canine recipients [44]. Their study reported normoglycemia in the canines for approximately 160 days, with one canine achieving euglycemia for 214 days [45].

Alginate converts into a gel form by ionic cross-linking with bivalent cations such as calcium, magnesium, and more commonly barium [46]. Cross-linking establish a mesh of porous material that allows bidirectional flow of materials, including oxygen, nutrients, and hormones (especially insulin). However, hydrogel polymerization does not result in uniform pore size, while internal permeability tends to vary between batches [38].

An increase in the degree of cross-linking results in gels that have superior mechanical strength but inversely reduces the size of the pores available for diffusion. It is possible to artificially organize the islets in alginate gels into clusters mimicking natural islets [47].

Surface modification using polycations and anions can change the permeability and mechanical strength of alginate, but the polarity tends to increase the immune response. Common molecules used for this purpose include: poly-d-lysine (PDL), polyethylene glycol (PEG), poly-L-ornithine (PLO), and poly-L-lysine (PLL). This effect can be counteracted by adding another layer of alginate to prevent direct contact with a polar surface [38], or by modifying the alginate [48].

Capsule fibrosis was the most significant problem encountered when utilizing alginate capsules [23, 49–51]. Theoretically, immune isolation is achieved by encapsulation of the cells, but some levels of immune rejection and foreign body response still occur. Also, while oxygen and nutrients are able to freely diffuse across a matrix, studies have shown that at the time of explant, histology showed a necrotic core in the encapsulated islets without evidence of fibrosis. This suggests inadequate oxygen diffusion into the center of the encapsulated islets [52].

The results demonstrated by these prior studies suggest that there are key points to be considered during engineering of the encapsulation vehicle. The raw and the purified capsule material must be nontoxic, while the purification method needs to be reproducible across batches. The polymerization of the capsule material needs to be noncytotoxic to the islets. If there is any degradation of the material, it must follow physiological tissue growth and its products must not adversely affect the coated cells or human body. For clinical application, it would be important for the capsule engineering to be easily scalable, while maintaining good manufacturing practices (GMP) adherence to satisfy regulatory standards.

4. Improvement on islet encapsulation engineering

4.1. Co-encapsulation

Co-encapsulation is the process of adding additional molecules to the capsule to enhance the performance of the encapsulated islets. Encapsulation of islets along with dexamethasone, a corticosteroid serving as local immune suppression, can improve islet survival in mice recipients compared to those islets alone [53]. In another study, co-encapsulation of mouse monocyte macrophage cells and hamster kidney cells with ibuprofen improved the encapsulated cell survival both *in vitro* and *in vivo* [54].

While encapsulation protects the cells inside from large molecules such as antibodies as well as direct cellular contact, smaller molecules such as pro-inflammatory cytokines can still diffuse across most hydrogel gradients due to their smaller molecular weight. To achieve this, an attempt

at islet encapsulation with a silicon nanopore membrane found observed cytokine protection and islet viability for over 6 hours, with the islets remaining responsive to glucose levels [55]. Thus, protection from these cytokines may promote capsule survival. In an *in vitro* study performed by Leung, capsules with anti-TNF alpha were able to remove active TNF-α, a pro-inflammatory cytokine from a culture medium, which resulted in better encapsulated cell survival [56].

4.2. Protection against hypoxia

In order to improve oxygen supply to the cell, access to a rich vascular bed is essential. Addition of the angiogenic factor, fibroblast growth factor 1 (FGF-1), into capsule was able to affect a continuous FGF-1 release for a 1-month period *in vitro* [57]. In another study, encapsulation of solid peroxide within polydimethylsiloxane resulted in sustained oxygen release from the matrix for approximately 6 weeks [58].

Extracellular matrix components, derived from laminin, have been shown to improve islet human islet function for encapsulated islet transplants. These extracellular matrix components are also found in native islets located in the pancreas prior to islet isolation. In this case, a variety of laminin-derived peptides or collagen were co-encapsulated with human islets and islet function was measured *in vitro*. Islet viability and insulin response to glucose were improved by the addition of laminin-derived peptide or collagen [59].

4.3. Prevascularization

Prevascularization of islet implant consists of establishing a well-vascularized matrix or scaffold, by implanting the scaffold, then encouraging angiogenesis that leads to scaffold penetration by microcapillaries. Angiogenesis is promoted by addition of fibrin at the time of scaffold implant. Islets were then added to the scaffold after a certain duration that has been shown to allow significant vascularization, as shown in **Figure 2**. This method was shown to improve subcutaneous islet efficacy in restoring normoglycemia when compared to subcutaneous transplants of islets alone [60].

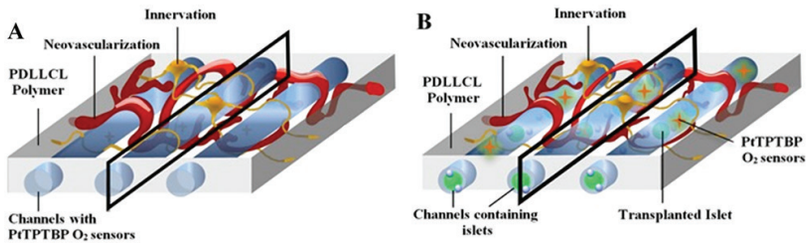


Figure 2. Prevascularized scaffold for islet transplant. Device is implanted subcutaneously 28 days before the introduction of the β-cell clusters during which the foreign body response and neovascularization are completed (A). The device contains polyethylene rods with high hydrophobicity to avoid cell adhesion. Upon removal of the rods, the islets can be infused (B).

4.4. Toward GMP standard

One of the key issues facing the engineering of encapsulating material for islet transplantation would be to define standards for the materials. The standards required contain the choice of raw material, the purification method and quality control of the purification, the shape of the device used for encasing the islets, and the quality of the encased islets. The lack of such standards is likely to account for the current variability in the results reported in the literature on the encapsulated islet transplant.

As an example of the standard necessary for clinical translation of the encapsulation technology, commercially available alginates used to create islet capsules have been found to contain pathogen-associated molecular patterns (PAMPS). PAMP such as peptidoglycan, lipoteichoic acid, and flagellin among other proteins, endotoxins, and polyphenols [61] can trigger recognition by the innate immune system. PAMPS are recognized by toll-like receptors (TLRs) and pattern-recognition receptors (PRRs) [61, 62], leading to pericapsular fibrotic overgrowth (PFO) [63] as the immune system attempts to isolate the graft. PFO severely hinders graft survival by preventing diffusion of nutrients and waste.

In addition to cellular adhesion and PFO, death of encapsulated islets may also be caused by chemokines and cytokines that are small enough to pass through the permeable capsules [64]. TLRs, upon recognition and binding of PAMPS to the receptor surface, initiate an intracellular signaling cascade ultimately resulting in the secretion of a host of inflammatory cytokines attributed to translocation of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) into the nucleus [65].

Before alginate can be used for clinical transplantation, it will need further development in the GMP manufacturing and purification of the raw materials, to ensure a low amount of PAMP detectable by the recipient's immune system. In addition, the production of the encapsulated islets, including the islet isolation and the encapsulation process, needs to achieve a threshold of standard of quality to ensure a consistent and reliable result, to make it possible to compare the effect of the variety of encapsulation techniques and improvements.

5. Conclusion

In this chapter, we have covered the variety of options used to protect transplanted islets physically against both transplant rejection and autoimmune assault on β-cells. The technologies covered include the variety of encapsulation devices, materials, and addition of supportive materials to improve islet function and survivability.

A key step toward translating biomaterial encapsulation of islets toward clinical trial would be to develop a standard of quality that has to be met by the raw encapsulation material, the islets, and the encapsulation process. This will eventually lead to a process that can be scaled up and to adhere to GMP quality requirements. The current variability of results in the literature on encapsulated islet transplants as T1DM treatment can likely be explained by the lack of such standard, making it impossible to reliably compare multiple encapsulation technologies.

The results in the literature on the encapsulation of islets for the treatment of T1DM showed that it is a promising technology that can revolutionize the treatment paradigm for diabetics. Although significant advances have occurred, there are several obstacles that must be addressed before achieving widespread use of this technology.

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