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Physical Protection of Pancreatic Islets for Transplantation

Sarah Lee, Mayilone Sathialingam,
Michael Alexander and Jonathan Lakey

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Abstract

Type 1 diabetes is an autoimmune disorder that destroys the insulin producing cells of the pancreas. The mainstay of treatment is replacement of insulin through injectable exogenous insulin. Improvements in islet isolation techniques and immunosuppression regimens have made islet transplants a treatment options for select patients. Islet transplants have improved graft function over the years, however, graft function beyond year two is rare and notably these patients require immunosuppression to prevent rejection. Cell encapsulation has been proposed for numerous cell types but it has found increasing enthusiasm for islets. Since islet transplants have experienced a myriad of success the next step is to improve graft function and avoid systemically toxic immunosuppressive regimens. Cell encapsulation hopes to accomplish this goal. Encapsulation involves encasing cells in a semipermeable biocompatible hydrogel that allows the passage of nutrients and oxygen however blocks immune regulators from destroying the cell thus avoiding systemic drugs. Several advances in encapsulation engineering and cell viability promises to make this a revolutionary discovery. In this chapter, we will provide a review of islet encapsulation as used for the treatment of type 1 diabetes.

Keywords: biomaterial, islet encapsulation, type 1 diabetes, islet transplantation, immune barrier

1. Introduction

Islet transplantation to treat type 1 diabetes has achieved great improvements, as more recipients are able to achieve insulin independence for longer periods of time. Unfortunately, the lack of donor organs and immunosuppressive medication regimens continue to impede further progress in cell replacement therapy. Encapsulation of islets for transplantation

provides a solution to these problems. Cell encapsulation envelopes cells in a biocompatible matrix that provides a gradient which allows the diffusion of oxygen and nutrients but prevents large immune molecules from reaching the cell, avoiding host immune response. Encapsulation has been suggested since the 1930s, but noteworthy achievements have occurred over the last decade. This chapter aims to provide a review including a historical background, current research, and future applications of cell encapsulation for the treatment of type 1 diabetes.

2. History

Over 25 million people in the United States (US) suffer from diabetes with approximately 5% characterized as type 1, and diabetes is ranked as the 7th leading cause of death in the US [1]. Type 1 diabetes mellitus (T1DM) is an autoimmune disease that causes destruction of the β -cells of the pancreas, which results in insulin deficiency [2]. Currently, the mainstay of treatment is short-term glycemic control through injectable exogenous insulin. However, as islet transplantation has been continually improving, the scientific community has shifted views of curing T1DM toward cell replacement therapy rather than supportive care. Islet transplantation was recognized as a promising field in restoring long-term endogenous insulin production when in 1999, under the Edmonton Protocol, a total of 21 subjects out of 36 were able to achieve long-term glycemic control and insulin independence upon transplantation of islets in the portal vein and the insulin independence prolonged up to 2 years [3]. According to the Collaborative Islet Transplant Registry (CITR), there have been a total of 677 islet transplant recipients from 1999 to 2010 and the percentage of recipients that achieve insulin independence for 3 years was 44% between 2007 and 2010 compared to 27% from 1999 to 2002 [4]. Various immunosuppressive regimens have been implemented to avoid rejection and maintain graft function. However, like other organ transplants, immunosuppressive medications are implicated in adverse effects to the patient as well as toxicity to the graft [5, 6].

Additionally, the current method for islet transplantation requires invasive, difficult, and time-consuming surgeries that create stress and risk for both the patients and the islets. To circumvent these issues, cell encapsulation has been proposed as the next treatment option for islet transplants with the goal of eliminating immunosuppression. Although cell encapsulation was tested to treat other diseases such as neurodegenerative diseases and epilepsy, the greatest achievement using this method has been in the encapsulation of islets for the treatment of T1DM [7–9]. Insulin independence can successfully be achieved through the transplantation of isolated islets; to ensure that the islets can remain effective and functioning, improvements in graft viability, difficulty of procedures, and the avoidance of systemically toxic drugs can be accomplished through encapsulation [10]. In the following sections, we will discuss the more recent advances in encapsulated islet technology.

3. Current research

3.1. Animal and human trials

The first researcher to pioneer transplantation of encapsulated tissue was Biscegele in 1933. He placed mouse tumor cells in a polymer matrix which he transplanted into the abdomen of a guinea pig and was able to maintain the host's survival without rejection [11]. This idea was replicated not until 50 years later when Lim and Sun first used encapsulated islets for transplantation in diabetic animals. They placed 2000–3000 islet equivalent (IEQ) in an alginate hydrogel for intraperitoneal transplantation of diabetic rats to achieve normoglycemia for up to 3 weeks compared to only 8 days for nonencapsulated islets [12]. Currently, there are a myriad of achievements in encapsulating islets in small and large animal studies as well as early phase clinical trials. In syngeneic transplantation (NOD mice) studies by Kobayashi et al. in 2003, the authors used a 5% agarose microcapsule encasing 1500–2000 islet equivalents (IEQ) per mouse for intraperitoneal implantation as well as omental pouch transplants, and observed prolonged euglycemia for 100 days compared to 8 days for unencapsulated islet transplants [13]. The same authors repeated the study in 2006 and observed the same period of euglycemia in the recipients; however, when they also retrieved the devices after 400 days, they observed that viable islets were recovered with a small percentage of necrotic cells [14].

In a more recent study of murine models, Nishimura et al. carried out a two-part experiment; the first experiment involved transplant of encapsulated porcine islets into the intraperitoneal cavities of streptozotocin-induced diabetic nude mice ($n = 4$) and observed insulin independence in all mice for 2 months. Then, to observe the long-term effects, the second part of the experiment involved the same procedure but required monitoring up to 6 months, and all mice had maintained insulin independence for the duration of the experiment although C-peptide levels were low for both experiments [14]. Encapsulation methods have improved over time, as shown in studies by Haque et al. in 2017, where non-human primate islets were encapsulated with polyethylene glycol (PEG) and confirmed functioning when transplanted into C57BL/6 and BALB/c mice. It was also observed that when compared to the naked islet transplant, the encapsulated islets had shown no graft rejection for up to 150 days [15].

Less consistent but otherwise noteworthy results were achieved in islet transplants in larger animal models. Initially, Soon-Shiong performed several encapsulated islet transplants into diabetic canine models. According to the publication from 1993, islets of 1500–20,000 IEQ/kg were encapsulated in alginate-based microcapsules and transplanted into the intraperitoneal cavity; subjects gained insulin independence for 110 days as well as the presence of C-peptide for an average of 483 days [16]. In 2010, Dufrane used porcine encapsulated islets (subcutaneous/kidney capsule transplants of alginate-based micro- and macro-encapsulated islets, 30,000 IEQ/kg) to transplant into cynomolgus primates. The authors observed euglycemia for up to 28 weeks [17]. In another study using cynomolgus monkeys as recipients by Elliott et al., neonatal pig islets were isolated (10,000 IEQ/kg) and encapsulated in alginate microcapsules resulting in a more than 40% reduction in injectable insulin dose compared to pre-implantation [18]. Based

on several noteworthy achievements in large animal studies, researchers have been granted approval for stage one and two human clinical trials. Due to the previous success by Soon-Shiong using a canine model the authors were authorized for the first human clinical trial in 1994. A 38-year-old male, with type 1 diabetes and end stage renal disease postoperative to kidney transplant and with low dose immunosuppression, became the first recipient of encapsulated islets. The patient initially received 10,000 IEQ/kg of cadaveric islets encapsulated in alginate microcapsules, followed by a repeat transplant of 5000 IEQ/kg 6 months later. The patient's insulin requirements reduced to 1–2 insulin units per day and eventually discontinued all exogenous insulin administration after 9 months [19]. In 2006, Calafiore et al. isolated islets from human cadavers (400,000–600,000 IEQ) and encapsulated them with sodium-alginate beads for intraperitoneal injection. As a result, the patients experienced improved blood glucose levels and a declined daily exogenous insulin intake; however, neither patient became insulin independent [20].

Living cell technologies has achieved the best outcomes for encapsulated islet transplants. In one of their studies, islets derived from pigs in a pathogen-free farm in New Zealand were encapsulated in alginate microcapsules for intraperitoneal xenotransplantation into human recipients. Several early phase clinical trials have been performed from this company and they have shown promising results. One of the most significant achievement has been the reduction of accidental hypoglycemic events to 40%. Several patients improved daily glucose levels and reduced exogenous insulin dosing and 2 patients became insulin independent after 4 months [21]. Despite the promising results, the lack of reproducibility threatens enthusiasm for future advances. For example, a human clinical trial by Tuch et al. involved alginate microcapsules for human cadaveric islets and observed the presence of plasma C-peptide levels for up to 2.5 years, however, there was no improvement in insulin requirements [22]. Likewise, in a follow-up publication by Elliot et al., one recipient experienced early success with a 30% reduction in insulin dose, but after 49 weeks, the subject reverted back to the original insulin dose [21]. The most recent study in 2016 by Matsumoto et al. which involved 8 human subjects, they did not observe statistically significant changes to the reduction of exogenous insulin doses; however, the group that received higher dose of islets had improved HbA1c (<7%) for a duration of 600 days, and had significantly reduced the frequency of unaware hypoglycemic events [23]. The study shows that despite the lack of insulin-secreting capabilities, as compared to exogenous injections which potentially and frequently cause accidental hypoglycemic events, the encapsulated islets are capable of a more regulated release of insulin. Although there has been a consistent observation of viability and immunoprotection of encapsulated islets, the efficacy of enabling a subject's insulin independence in-vivo is still being researched.

Although the purpose of aforementioned early phase clinical trials is to assure safety and determine optimal dosing, it is notable that most encapsulated islet recipients do not achieve perfectly sustainable insulin independence. There is also yet to be a standardized protocol for the type of biomaterial used and the islet dose to be transplanted. However, based on novel in-vivo studies, it is evident that the type of biomaterial determines graft survival. King et al. tested several encapsulation methods for mice recipients using alginate with and without poly L-lysine (PLL), with high guluronic acid (G) or high mannuronic acid (M) and revealed

that PLL-free high M microcapsules had better results, with continuous normoglycemia for 8 weeks [24]. Likewise, Lanza et al. observed that capsule integrity and graft function could be improved by altering the concentration of alginate [25]. More recently, hyaluronic acid and collagen hydrogels (HA-COL gel), which have been steadily gaining recognition in tissue engineering, have taken a new turn and started emerging as a potential alternative to alginate for encapsulation material for islets. In 2016, Harrington et al. had proposed that HA-COL gels' biological and mechanical properties can be applied to encapsulating methods of islets as well, and in the study, they observed that the allogeneic transplantation of islets in HA-COL gels into diabetic rats had reversed diabetes and remained such for 80 weeks, all while providing immunoprotection for islets and increasing viability [26]. Discussions regarding the most optimal material for encapsulation of islet are still ongoing, and a definite consensus is yet to be reached.

3.2. Biomaterials in transplantation

Chang et al. were the first researchers to describe the application of semipermeable membranes for encapsulation. Chang postulated that polymer membrane-encapsulated liver enzymes and cells can be transplanted to treat a disorder [27]. Several types of encapsulation methods have been developing and currently the most widely employed method is the alginate-based microencapsulation [24, 28–30].

The capsule vehicles come in variety of structures and sizes, ranging between vascular shunts, macro-, micro-, and nanoscale devices. The original vascular device was developed as capillary fibers in culture-coated medium [31]. Maki et al. performed studies with vascular devices as arteriovenous shunts transplanted in diabetic canines. As a result, several subjects were able to achieve reduced exogenous insulin requirements [32, 33]. Ultimately, the major difficulty in utilizing the devices was the inability to provide enough islets to coat the fibers. This device type was able to achieve reduced exogenous insulin requirements [32, 33].

Devices were constructed in hopes of including more islets by elongating fibers, but complications arose due to clotting and fibrosis. To solve this issue, researches used greater amounts of islets and multiple devices in order to achieve insulin independence, but this method was eventually disused due to its high cost and relative inefficiency [34]. However, a 2017 study demonstrated the potential of human recombinant antithrombin (ATryn®), when co-administered with pancreatic islets, to reduce inflammation and intravascular coagulation in transplant recipients without posing a risk to the islets or test subjects [35]. In general, macroscale devices are not as commonly used among researchers because their increased immunogenicity and larger diffusion parameters required for oxygen and nutrients to reach islet cells lead to poor islet viability, function, and regenerative capacity [36]. However, such macroscale devices can offer several advantages, including simple implantation and retrievability using minimally invasive techniques [37]. One recent study elaborated on the ability of alginate sheets to promote vascularization and blood flow to areas of implanted sheets in mice due to a robust vascular response in the host. In response to increased blood flow and

consequently more oxygen and nutrients reaching the islets, the islets in the alginate sheets maintained high viability and function [38]. In a later attempt to improve the diffusion of nutrients, glucose, and insulin in cells in macroscale devices, a novel macroencapsulation device was developed in which islets were placed in thin, nondegradable, microwell membranes of the device. The results reveal that the device was effective in maintaining islet responsiveness and function in cell culture. However, future studies need to be conducted to test the in-vivo success of such a device [39].

Nanoencapsulation has been used to improve diffusion parameters and better islet insulin response. PEG is one of the most common materials used in nanoencapsulation devices as it can crosslink under UV or visible light exposure without threatening cell viability. Nevertheless, the shortcomings of PEG include the lack of biocompatibility with the transplant recipient and inadequate protection of islets from cytokines [40]. However, by using multi-layer PEGylation and immunosuppressive drug cocktails, islets have demonstrated increased stability and longer survival time while minimizing the immune response, as indicated by the reduction in human serum albumin, fibronectin, and immunoglobulin G [41]. In a 2017 study, majority of diabetic animals that received a transplant of PEGylated islets exhibited long-term normoglycemia [42]. Thus, despite its shortcomings, PEG encapsulation has still yielded positive results in certain studies.

Despite the success of nanoencapsulation, microencapsulation still is the most widespread method of islet encapsulation due in part to their improved surface area to volume ratio and mechanical stability. Though biocompatibility issues still exist with microencapsulation, the spherical shape and spatial characteristics of microcapsules can promote the diffusion of nutrients while limiting the host immune attacks on transplanted islets [43, 44]. One major obstacle standing in the way of sustainable and consistent clinical islet transplant is the lack of an optimal cell encapsulation approach, particularly the ideal transplantation site, encapsulation material and encapsulation device. Such standardization, as well as safety and cost effectiveness, are imperative for future widespread clinical use. Numerous tests have been conducted regarding various encapsulation materials and methods, each study showcasing the effectiveness of different encapsulation materials [43].

Both synthetic agents, from poly ethylene oxide to poly vinyl alcohol, and natural occurring hydrogels, like gelatin, chitosan, and alginate, have been utilized in encapsulation engineering and in extracellular matrixes [45–47]. Though poly glycolic and lactic acid polymers are some of the more popular synthetic agents in medical devices, they still pose the risk of increased fibrosis and loss of the encased cells. Nevertheless, synthetic biomaterials are still being frequently used, with PEG being the most widely used synthetic biomaterial for islet encapsulation, though different encapsulation strategies have varying levels of success. Such strategies include assembling a thin layered PEG-lipid structure around the surface of islets and assembling a multilayer film around islets using biotin and streptavidin [48]. It has been recently demonstrated that the simple PEGylation of islets provided modest immunoprotection in full MHC mismatched mice [42]. However, when coupled with the systematic distribution of immunosuppressive drugs, the PEGylated islets could sustain long-term normoglycemia in the mice.

Due to the complications with islet encapsulation using synthetic materials, alginate encapsulation has risen in popularity due to its improved biocompatibility and stability, easy gelation process, and relatively low cost. Alginate has typically been the most popular microencapsulation material, due to its widespread availability and ease of production, although alginate endotoxin content and purity can vary from different manufacturers [44]. The variation in alginate production and purification, in addition to the lack of research regarding the optimal transplantation site of islets and optimal donor strain and age, currently stand in the way of consistent success in transplanting alginate encapsulated islets into humans [49]. In an effort to improve capsule permeability and mechanical strength, studies have used polycations and anions in the encapsulation process, although it often results in a greater host biologic response to the transplant. To resolve this issue, one study discovered that this immune response can be minimized with the addition of another thin layer of alginate [50]. During the process of gelation, cross linking occurs via covalent, ionic, or physical bonds, which subsequently establishes the diffusion gradient for the adequate flow of nutrients and oxygen to the islet cells. Previously, problems with crosslinking arose in regard to such capsules having smaller pore size with inconsistent permselectivity [50]. However, in a recent study, alginate capsules crosslinked with BaCl_2 and suspended in chitosan showed similar pore size, function, and viability *in vitro* when compared to regular alginate capsules. When islets were encapsulated in the chitosan-coated crosslinked capsules and transplanted into mice and canines, the islets improved in graft survival and had significantly less fibrosis when compared to regular alginate capsules at 1 year post-transplantation [51].

When engineering scaffolds for islets, there are multiple considerations that need to be taken before standardizing a procedure that is both practical and safe for the islets and host. The capsules need to be non-toxic and reproducible, and their degradation should not negatively affect the islets or host, but rather following tissue growth.

Earlier experiments regarding capsule construction encountered problems with capsule fibrosis and low islet viability and function. For example, extensive capsule fibrosis was a common occurrence in these early experiments [22, 52]. Subsequent studies were able to eliminate the presence of fibrosis, but at the expense of abundant necrotic islets due to inadequate oxygen flow to the transplanted islets [53, 54]. However, multiple potential solutions have been explored since these issues were encountered. As a preliminary solution to high capsule fibrosis and lack of oxygen supply for transplanted islets, a group of scientists created a highly-vascularized bioartificial cavity using polylactide-based scaffolds for islet transplantation and implanted it under the skin and in the omentum of rats. After 4 weeks, histological analysis revealed heightened vascularization with minor fibrosis and minimal infiltration of inflammatory cells near the implant [55]. In a different experiment aimed to improve the oxygen flow to transplanted islets, a bioartificial pancreas underscored the potential of HEMOXCell® as an oxygen carrier for islets *in vitro*. HEMOXCell® was able to increase cell viability and decrease hypoxia indicators while restoring insulin secretion back to normal levels [56].

Other researchers have gone on to improve capsule engineering by means of co-encapsulation and stem cells to reduce instances of inflammation and fibrosis while sustaining islet function.

3.3. Improved capsule engineering: Co-encapsulation

Co-encapsulation methods hope to enhance the viability and function of islets by adding molecules to the capsules surrounding the cells. The essential purpose of encapsulation is to suppress the host animal's immune response to reduce inflammation and increase the survival of islets. In a novel study, the co-encapsulation of HMGB1 A box protein, an inflammation receptor antagonist, with islets provided a protective effect in islet transplants; the results showed an a 2-fold improvement in the survival rate of such co-encapsulated islets in diabetic mice. These islets were similar in bead diameter, viability, and insulin secretion function to islets encapsulated in only alginate [57]. In another study investigating co-encapsulation techniques to reduce inflammation, scientists conducted a subcutaneous screening of 16 small anti-inflammatory drugs to see each drug's corresponding effect on the formation of fibrotic cell layers, of which dexamethasone and curcumin showed to be most effective. Subsequently, pancreatic rat islets were co-encapsulated with curcumin in alginate microcapsules, resulting in an increase glycemic control and reduced instances of fibrosis in diabetic mice [58]. Clearly, co-encapsulation can be effective in reducing the recipient's immune response. However, researchers have not limited themselves to only co-encapsulation research, as recent developments in encapsulation cell technology involves the use of stem cells as a source of islets.

3.4. Stem cells

Due to the lack of human cadaveric donors for islet transplants, stem cells provide a promising alternative for islet transplants. In a study by Vaithilingam, mesenchymal stem cells were stimulated by a cytokine cocktail of IFN- γ and TNF- α and subsequently were co-encapsulated with islets and transplanted into mice. All of the mice attained normoglycemia, as opposed to just 9.1% of the mice that received alginate encapsulated islets. In another study, mice receiving co-encapsulated stimulated MSCs also demonstrated improved viability and function with significantly less inflammatory cytokines, a significant step forward in the search to optimize encapsulated islet transplants [59]. A minimal immune response was also achieved in abdominal transplants using MSC islets coated luciferase-GFP, with reduced fibrotic formation and macrophage infiltration. Furthermore, islet endothelial cells formed chimeric blood vessel in the surrounding tissue with the transplant recipient's cells, due to the presence of MSC [60]. In another study, pancreatic islets were encapsulated using a silk-based platform including MSCs, resulting in the reduction of Th1 cytokines and improvement in blood glucose response. However, future experiments need to evaluate the viability of the islets and methods to strengthen the biocompatibility of silk for transplantation purposes [61]. Most importantly, a recent study demonstrated that an autologous stem cell transplant was able to accomplish long-term sustainable insulin independence in humans diagnosed with T1D, a phenomenon that had not occurred in previous decades [62]. Findings like these demonstrate the vast potential of stem cells in islet transplants, with more improvements bound to occur in the upcoming years.

4. Conclusion

Recent discoveries in the cell encapsulation of islets have made great strides in the pursuit to revolutionize the current treatment for T1DM. These studies have made significant

advancements to improve islet viability, function, and insulin response to higher blood glucose levels in transplanted islets. However, multiple obstacles still stand in the way of standardizing a method to allow widespread clinical use of this technology. Nevertheless, improvements in islet encapsulation materials and methods, as well as the growing potential of co-encapsulation and stem cell use for islet transplants provide a promising future in this field of research.

Author details

Sarah Lee¹, Mayilone Sathialingam¹, Michael Alexander¹ and Jonathan Lakey^{1,2*}

* Address all correspondence to: jlakey@uci.edu

¹ Department of Surgery, University of California Irvine, Orange, CA, USA

² Department of Biomedical Engineering, University of California Irvine, Irvine, CA, USA

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