The Holy Grail of Tissue Engineering? Islet cell microencapsulation in type 1 diabetes mellitus

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Abstract

The immunoisolation of transplanted islet cells represents a promising future therapy for the treatment of type 1 diabetes mellitus (T1DM). Microencapsulation is one avenue being explored to restore insulin independence while simultaneously protecting islet cells from destruction by the immune system. A variety of techniques have been developed to encapsulate the islet cells, with alginate being the most commonly employed biomaterial. The great challenge in microencapsulation is to ensure that the capsule is permselective, allowing for the free diffusion of oxygen, nutrients and waste products while providing an effective barrier to cytokines and immune identification. Other alternatives including nanoencapsulation and conformal coating are emerging. In vivo work is now beginning to be translated into clinical trials.

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by pancreatic β-cell destruction and an absolute deficiency of insulin. Affecting over 500,000 children under 15 worldwide, the International Diabetes Federation estimates that an additional 79,000 children developed type 1 diabetes in 2013[1, 2].

Over the last decades, clinical islet transplants have emerged as a possible therapy to replace those originally destroyed. In the early 1990's, 7 patients were transplanted with pancreatic islet cells and remained insulin independent for an average of 12 months[3]. The Edmonton protocol, a method of islet cell transplantation that uses immunosuppressive medications, developed as a result of this success and remains the current standard[4]. Islets are saved from destruction by the immune system through the usage of a concoction of various immunosuppressive agents. However, there are a whole host of adverse effects of immunosuppressive drugs including, but not limited to, an increased susceptibility to illness and cancers.

The possibility of transplanting an endogenous insulin source into a diabetic patient to control their blood sugar is one of the holy grails of tissue engineering. One of the more commonly used procedures for immunoprotection of transplanted tissues is the microencapsulation of islets in an alginate-based capsule[5]. This procedure was originally described by Lim and Sun but in recent years important advances have been made to bring this technology from beyond the realms of science fiction[6]. With the commencement of human trials, temporary but significant survival of human microencapsulated tissue has been observed[7, 8]. One substantial hurdle that has to be overcome is the issue of the variability of graft survival[9]. A wide variety of approaches have been used to improve capsule properties.

Why encapsulate?

The concept of islet microencapsulation is to create a permselective membrane around a cluster of islet cells using an immunoprotective biomaterial. Ideally the encapsulation should eliminate, or at least limit, any immunological response to the graft.

Allowing for the clinical use of xenogeneically-derived islets or engineered insulin-secreting stem cells, encapsulation may offer a solution to the shortage of donors for clinical islet transplantation.

Encapsulation devices to date generally range from microscale to macroscale devices. Macrocapsules can be up to 3cm by 8 cm and hold up to 250 µL of tissue[10]. In contrast, microcapsules are droplets ranging from 100 nm to 1mm in size[11,12]. To optimize oxygen and nutrient delivery and waste removal, ideally capsules would be placed intravascularly. However, this strategy has been, in the main, abandoned due to the increased risk of thrombosis and haemhorrhage[13]. The membrane that encapsulates the islets should be porous enough to allow diffusion of glucose, insulin, oxygen and other nutrients while remaining selective enough to omit immune cells, toxic cytokines, complement proteins and cytokines[14].

In microencapsulation, individual or small clusters of islets are incorporated into a spherical hydrogel polymer formed through various techniques. This offers improved diffusion capacity due to a better surface/volume ratio[15]. Another major advantage of microencapsulation is that individual islets are protected from any immune attack. This means that, as long as the failure rate is kept low when forming the microcapsules, only the affected islets will be destroyed. However, if there is a small failure rate in a macroencapsulated device, the whole population of encapsulated islets is at risk of destruction[16]. One downfall of microencapsulation to date has been their sometimes very large size in comparison to the islets or groups of islets contained within. This may result in capsules made up predominantly of hydrogel with only a comparatively, very small amount of islets.

CLINICAL POINTS

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Over the last decades, clinical islet transplants have emerged as a possible therapy to replace those originally destroyed

With microencapsulation, individual or small clusters of islets are incorporated into a spherical hydrogel polymer that offers improved diffusion capacity and immuno-protection

In in vivo animal and human models, transplanted encapsulated islet cells can survive when placed in the peritoneal cavity. These transplantations could reduce the requirement for exogenous insulin injections

Issues that need resolving include optimization of insulin release and further data on the length of functional survival of microcapsules once implanted. Further in vivo animal models and extensive clinical trials are required to optimize and evaluate this therapy

In vivo studies

In a recent pilot study, Jacobs-Tulleneers-Thevissen and colleagues showed that transplanted human islets contained within alginate microcapsules could reverse diabetes in mice when placed in the peritoneal cavity[41]. These encapsulated cells performed significantly better than non-encapsulated cells implanted under the fibrous capsule of the kidney[41]. The microcapsules were retrieved after 5 weeks and found to have retained functional, healthy, insulin secretory responses to glucose and glucagon stimulation. This was in contrast to the non-encapsulated cells which were found to be completely non-functional and only retained 10% of their initial β-cell population[14,41].

Barium-alginate microbeads have been the most extensively studied non-coated alginate beads for microencapsulation. One group, using an in vivo T1DM model, managed to normalize the blood glucose of a non-obese-diabetic (NOD) mouse over the course of one year using allogenic islets embedded in barium-alginate microcapsules[17]. The protection of these uncoated beads was effective in T1DM and it was believed that the encapsulated islets may survive for longer than a year[17]. The group also suggested that regeneration of islets occurs within the capsules as the average life span for a β-cell is 3 months[18].

An encapsulated islet allotransplantation was first performed as a clinical trial in a 38 year old T1DM male. Human islets isolated from a cadaveric pancreas were encapsulated in alginate microcapsules. They were then injected into an intra-peritoneal location at a dose of 10,000 islet equivalent per kilogram (IEq/kg) body mass with a booster of 5,000 IEq/kg six months later. The patient was able to survive purely from the endogenous insulin secreted from the implanted islets for a period of nine months proving that encapsulated islets are capable of achieving adequate glycemic control in a T1DM subject. However, one aspect of this particular case worth noting is the fact that this man was already on an immunosuppressive regimen prior to receiving the transplanted islet[20]. Thus, it was not possible to state whether or not the alginate microcapsules offered any immune protection to the encapsulated islets. A follow up study done in four more T1DM patients transplanted with microencapsulated islets displayed a statistically significant decrease in insulin requirements for several months. However, at follow-up seven years later all patients were entirely dependent on exogenous injections of insulin again[19]. Similar results were noted in a separate trial where two patients were implanted with islets encapsulated within alginate microcapsules. Both patients had significant reductions in their insulin dosage requirements but complete insulin independence was never achieved[20].

One potentially promising product currently in clinical trials is the Diabecell by Living Cell Technologies. This is an alginate-based microcapsule for the implantation of pig islets[21, 22]. Viable encapsulated porcine islets were reported after a 9.5 year laproscopic biopsy in one patient. Another trial of the same product in Moscow in 2008 found that 2 out of 3 patients receiving 10,000 islet equivalent per kilogram (IEq/kg) body mass were insulin independent 6 months post implantation[23]. Another trial also had its subject have his islets inspected under laparoscopy. Although this patient still had a detectable C-peptide level, his encapsulated islets were not producing enough insulin to attain control of his diabetes. They were found to be surrounded by a fibrous tissue and some of the islets necrotic[11].

Challenges in islet microencapsulation

Studies have frequently reported that the kinetics of insulin are delayed when islets are microencapsulated. This appears to be related to microcapsule volume[16]. Perfusion work performed in vitro has shown that insulin is released 10-15 minutes earlier from cells that are not encapsulated as compared to microencapsulated islets. There is a parallel delay in the return toward basal rates when concentrations of glucose decrease from high to low values.

The kinetics of insulin release may also be affected by its anatomical placement during surgery. Often an intra-peritoneal location is chosen. If the encapsulated islets fail to adhere to the recipient's tissues then, when the recipient assumes an upright position, the capsules may fall into the pelvis. The oxygen carrying capacity of the peritoneal fluid is quite low and thus, a large amount of the encapsulated islets die off when packed into the pelvis of primates[16]. However, if the microcapsules are adequately adhesive, they will resist falling into the pelvis[16].

Sufficient supply of oxygen and nutrients is crucial to the longevity of islets. For effective oxygen and nutrient transfer, islets cannot be located more than 200 µm from capillaries[24]. There is no convection movement within the microcapsule and thus a nutrient gradient is induced from the capsule surface in to the islet centre[25, 26]. One obvious solution to combat this apparent nutrient-gradient would be to reduce the capsule size. However, there are significant disadvantages to reducing capsule thickness as the number of capsules that contain islets that are partially protruding will proportionally increase[27,

[28]. Thus, the number of microcapsules affected by an inflammatory response would also increase.

Many studies initially assumed a loss of 2-10% due mainly to the reasons mentioned. What could not be explained, however, was the failure of the remaining 90-98% of the capsules[29, 30]. It was unclear what was causing failure since it was generally assumed that the loss of 2-10% of capsules cannot explain the failure of the cells in the remaining 99-90% of the capsules[29, 30].

However, new insight has been brought to the situation over the last number of years. In a series of experiments it became clear that it was the islet cells (as opposed to any failing of the biomaterial) that was at fault for the failure. Cytokines such as MCP-1, MIP, nitric oxide, and IL-6 are secreted by islet cells when stressed[31]. These cytokines recruit and activate immune cells[31, 32, 33]. A follow-up experiment showed that activated macrophages surrounding the 2-10% of overgrown capsules secreted IL-1β and TNF-α when co-cultured with microencapsulated islets but not with capsules that are empty[32, 33]. IL-1β and TNF-α are known to place islets under stress. A progressive loss of function of the encapsulated tissue was observed[33, 34]. Essentially, this series of experiments showed that cytokines derived from the graft diffuse out of the capsules, activating macrophages which go on to secrete cytokines in a feed forward cycle.

What is it that sets off this destructive cycle? Transplantation of microencapsulated cells into the peritoneal cavity requires just minor surgery. However, this procedure is still associated with an element of tissue damage. Chemotactic proteins such as fibrinogen, thrombin, histamine and fibronectin are released[35]. An influx of large numbers of inflammatory cells (granulocytes, basophiles, mast cells, and macrophages) is induced into the peritoneal site in the early days after the implantation procedure[36].

In the first months after transplantation, the release of bioactive factors from the encapsulated tissue is responsible for the loss of 60% of the engrafted tissue[29]. The diffusion of graft-derived and inflammatory cell-derived cytokines is a major threat for the longevity of the encapsulated grafts[37]. One potential way of overcoming the issue of islet-derived cytokines is to reduce the permeability of the capsule. However, how is it possible to protect against harmful cytokines with a similar molecular weight to insulin or other vital nutrients (5-15kDa)? Up until recent years it was thought that this diffusion of cytokines into capsules was an impossible barrier to adequate immunoisolation.

Interestingly, several studies have shown this to not be the case. The ultimate effect of cytokines depends on a combined presence of various cytokines and on the concentrations of these respective cytokines[32, 33, 38]. In vitro, it has been shown that by decreasing the permeability via chemical modification, it is possible to prevent large, multimeric cytokines such as TNF-α diffusing into the capsule. Another group showed that damage induced by cytokines is minor in 'medium size' (400-500 µm) microcapsules and increases in smaller microcapsules[39]. With respect to immunoprotective capacity, this observation tends to suggest that microcapsules may display superior performance than conformal coatings (whereby a thin protective chemical covering or film is used)[39].

An interesting revelation in recent years has been the fact that, in the case of xenografting encapsulated islets in humans, cytokines may not interfere with islet functioning to the same extent as allografting. This is due to the fact that xenogenic islets (i.e. islets derived from a different species) do not readily bind to and take up human cytokines[40]. The implication of these findings is that xenogenic islets will be less affected if encapsulated in a cytokine-permeable biomaterial5.

Microscale cellular encapsulation methods allow for the precise control of cell size and shape. However, the scale-up to mass production using cost-effective and labour-efficient methods and automation represents another great challenge for the future.

Discussion

The idea that implanted islet cells can be protected from immune system identification and destruction through the use of a permselective biomaterial barrier remains an attractive therapeutic approach in spite of the challenges being faced. Advances in the clinical translation of laboratory research have somewhat slowed down since the initial great pioneering developments in islet transplantation. However, an appreciation for the subtleties and nuances of the diffusional characteristics of the encapsulating material combined with an improved understanding of the workings of the cytokine and complement systems has led to a renewed interest and enthusiasm in the field.

It has been shown in vivo animal and human models that transplanted encapsulated islet cells can survive when placed in the peritoneal cavity. In a growing number of instances these transplantations have reduced the requirement for exogenous insulin injections. However, one issue that needs resolving is how long can encapsulated islet cells survive and function when transplanted? There is a great degree of discordance in the literature on the lifetime of microencapsulated islets. In its current form, islet encapsulation appears to be at most a medium-term solution for patients as grafts appear to be functionally useful from several months to just over a year. Most likely, if this becomes a therapeutic option, patients may need to replenish lost islets with annual 'top-ups'.

Another issue affecting islet microencapsulation is whether or not the kinetics of insulin release will be adequate. The choice of anatomical location may need to be optimized in future to ensure that there is an appropriate vasculature for insulin levels to rise and fall quickly either side of meals while, at the same time, allowing for minimally-invasive delivery. The biomaterial encapsulating the cells also requires further optimization to ensure that oxygen, nutrients and waste products can freely diffuse in and out of the capsule, avoiding any 'nutrient-gradients'.

New techniques for islet encapsulation are beginning to show promising results. Further in vivo animal models and extensive clinical trials are required to optimize and evaluate this therapy. Islet transplantation is potentially the most important advance in the treatment of T1DM since Fredrick Banting and Charles Best discovered insulin in 1921. With the possibility of significantly improving the quality of life of patients and, essentially, even curing the disease itself, it is hard not to be at least cautiously optimistic about what the future has in store for islet cell microencapsulation.

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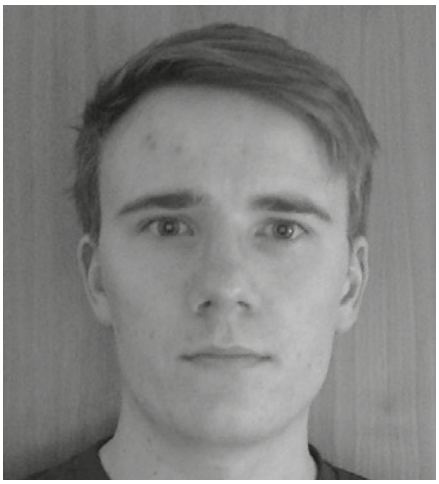

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