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Review

Biohybrid Devices and Encapsulation Technologies for Engineering a Bioartificial Pancreas

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The use of cell-based treatments in the field of metabolic organs, particularly the pancreas, has seen tremendous growth in recent years. The transplantation of islet of Langerhans cells for the treatment of type 1 diabetes mellitus (T1DM) has allowed for natural glycemic control for patients plagued with hypoglycemia unawareness. The transplantation of islet cells into the portal vein of the liver, however, has presented challenges to the survival of the cells due to inflammation, vascularization, the need for systemic immunosuppression, and physical stress on the graft. New advances in the engineering of appropriate biohybrid devices and encapsulation technologies have led to promising alternatives to traditional methods.

Key words: Diabetes; Bioartificial pancreas; Biohybrid device; Encapsulation

INTRODUCTION

Cellular transplantation has long been regarded as the ideal treatment of insulin-dependent diabetes. Due to the inherent complexity of these metabolic cells, efforts to mimic their functions using supplemental methods, such as exogenous insulin injections and pumps, have been inadequate. The scarcity of donor organs and the complexity of transplants have forced researchers to investigate novel methods within the field of tissue engineering for fabricating bioartificial, cell-based organs. Recapitulation of a pancreas through the application of tissue engineering principles is faced with many unique challenges. Due to the high nutrient demand and the need to retain intimacy with the surrounding environment for adequate function, the development of devices and/or encapsulation technologies that meet this need is problematic. In spite of these challenges, a recent focus on the development of biohybrid devices and encapsulation methods that are specifically tailored to the needs of these highly specialized and sensitive cells has resulted in progression of the field.

BIOHYBRID DEVICES

Macroscale biohybrid devices for engineering a bioartificial pancreas are typically designed to provide structural integrity to the implant, mechanical protection to the cells, encourage positive cell-to-cell or cell-to-matrix interactions, and provide ease of implantation and/or retrievability. Due to the high metabolic demand of islets, up to 10^6-fold higher than chondrocytes (11, 36), the confinement of these cells within a defined space presents a significant obstacle. Therefore, traditional biohybrid devices are inefficient in nutrient delivery, leading to significant cell loss. Second-generation devices designed to reduce cell loading density, however, typically result in devices too large to permit human-scale implantation. Recent focus has been on the redesign of macroscale biohybrid devices that promote

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vascularization and effective nutrient delivery to prevent islet cell necrosis and to minimize device volumes.

One strategy in biohybrid design is focused on the fabrication of a prevascularized site, which allows for the development of a complete vascular bed prior to implantation of the transplanted cells. This approach is ideal because the islets are not exposed to an extended phase of inadequate nutrient delivery and exposure of the islets to inflammatory agents commonly upregulated during neovascularization is minimized. The development of a prevascularized site for cell transplantation allows for the adaptation of a site from one that is not supportive of cell transplantation to one that is adequately perfused. For example, the subcutaneous site is a desirable implantation site primarily due to its ease in accessibility for both transplantation and retrieval; however, it is not ideal due to mechanical stress and delayed vascularization. The use of highly porous cages as shells for providing mechanical protection and guiding neovascularization has been published by Pileggi et al. (29) and Halberstadt et al. (10). In both cases, the cage was fitted with a plunger during the initial phases of implantation. At the end of the prevascularization period, the plunger was removed and islets were implanted within the void space. While the device confers no immunoprotection from the host, the outer cage provides mechanical support and a fully developed vascular bed to supply nutrients efficiently. In addition, the ability of the vasculature to infiltrate the device and, in turn, the islet, leads to islet revascularization, a condition that is highly desirable to achieve efficient nutrient delivery and minimize islet necrosis due to poor oxygenation (13). For both cases, the biohybrid devices exhibited engraftment efficiencies and function similar to standard implantation sites, such as the liver and renal subcapsular site.

Macrodevices, such as hollow fibers, have also been used as initial shells for subsequent cell loading. The use of biomaterials, as opposed to metal cages, allows

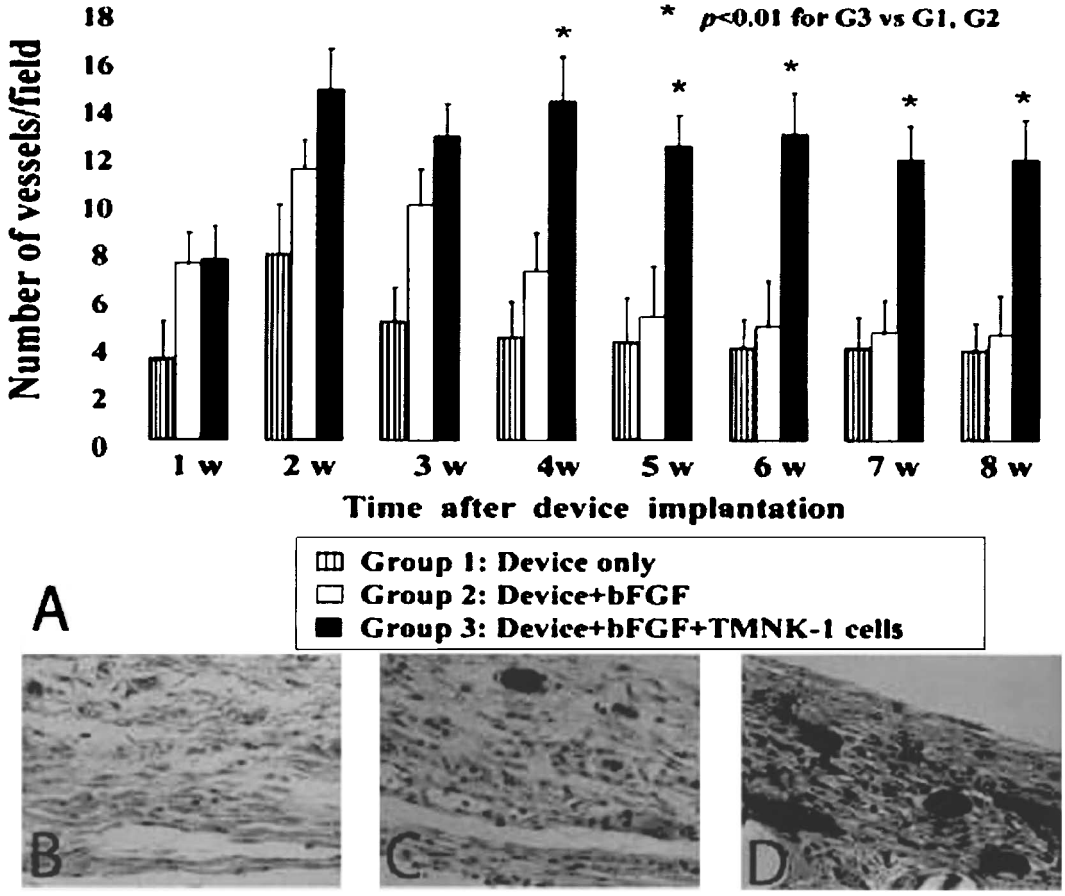

Figure 1. Quantification of neovascularization in the subcutaneous tissue surrounding the implanted BAP device (A). The number of vessels per field was histologically determined for each group. Representative histological images of the subcutaneous tissue at the implantation side of the BAP device for Device only (B); Device + bFGF (C); and Device + bFGF + TMNK-1 (D) experimental groups. Reprinted from Miki et al. (23) with permission from Cognizant Communication Corporation.

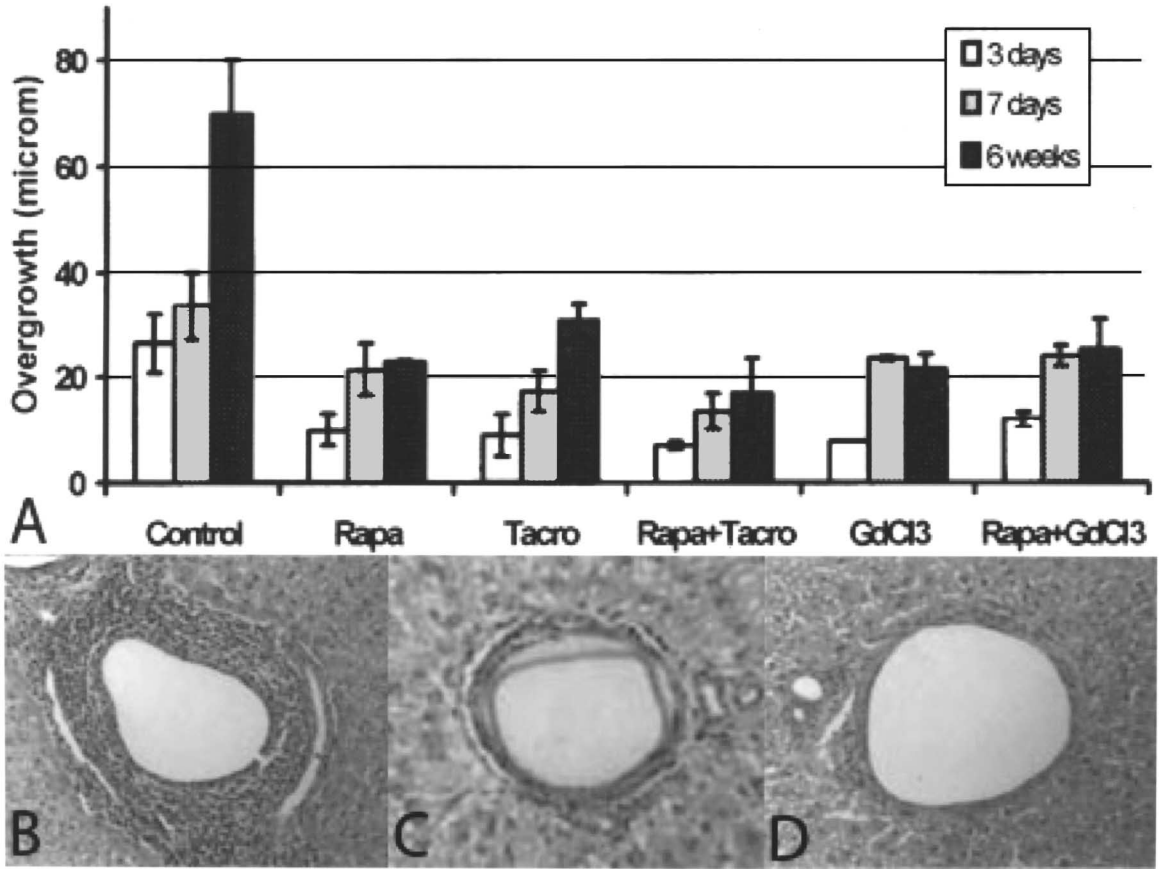

Figure 2. (A) Quantification of reduction of pericapsular overgrowth thickness at 3 days, 7 days, and 6 weeks after microbead implantation, without (Control) or with short-term immunosuppression of PO rapamycin 1mg/kg/day on days 1–10 (Rapa), PO tacrolimus 3 mg/kg/day on days 0–10 (Tacro), a combination of rapamycin/tacrolimus on days 1–10 (Rapa + Tacro), IV gadolinium-chloride 20 mg/kg/day on day −1 and 4 (CdCl3), or rapamycin/gadolinium (Rapa + GdCl3). Representative histological images of pericapsular infiltration around control (B), PO rapamycin (C), and PO tacrolimus (C) treated implants following 7-day implantation. Reprinted from (34) with permission Cognizant Communication Corporation.

for additional flexibility in parameters, such as surface properties, porosity, and the incorporation of angiogenic factors, to assist in accelerating neovascularization. For example, as illustrated in Figure 1, accelerated angiogenesis was observed following the subcutaneous implantation of a biohybrid device comprised of ethylene vinyl alcohol (EVAL) membrane coated with basic fibroblast growth factors (bFGF) and a human liver vascular endothelial cell line, TMNK-1 (23). The combination of these two treatments increased vasculature and blood flow around the bioartificial pancreas device compared to control implants. Supplementation of angiogenic growth factors was also shown to improve vascularization for other macroscale devices (30,35). In another approach, Lembert et al. fabricated rough, highly porous capillaries from highly hydroxymethylated polysulfone as a means to direct and promote vascularization to a macroscale device (21). These implants were found to exhibit improved vascularization in the presence of islets.

Other researchers have also investigated the use of arteriovascular shunts to serve as a means to immediately access convective nutrient delivery and avoid a two-step transplantation protocol. Examples of these methods include the implantation of biohybrid devices within surgically fabricated AV-loops and shunts (2,28).

MICROENCAPSULATION

Immunoisolation of transplanted cells from the host, typically via encapsulation, is a long desired technique for minimizing the immune response and the subsequent need for high-dose immunosuppressive protocols, which are associated with serious side effects and impaired function of metabolic cells (27). By coating the surface of a cell with a semipermeable biomaterial, the ability of host cells to recognize surface antigens of the im-

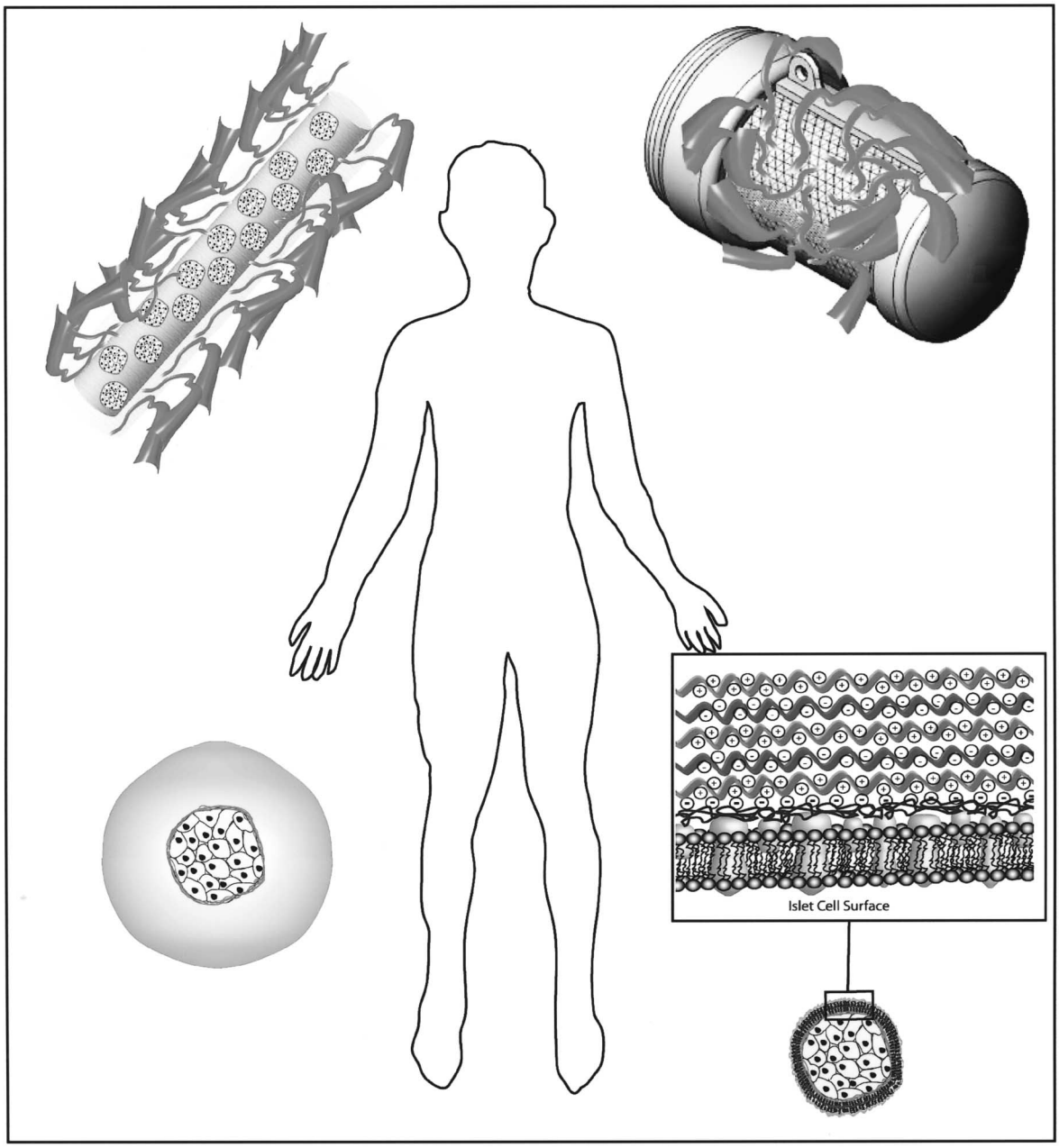

Figure 3. Schematic representation of devices in development as a bioartificial pancreas, including (clockwise from top left) the vascularized hollow fiber, vascularized biohybrid chamber, nanocapsule, and microcapsule.

planted cells is impaired. Furthermore, by providing a barrier between the host and the transplanted cells, direct cellular attack by the host is prevented. By masking immune recognition, encapsulation also opens up the possibility of xenotransplantation as a means to circumvent the shortages in human islets for transplantation. Biomaterials used for encapsulation should be highly biocompatible, stable, inert, and of a sufficient porosity to not interfere with the encapsulated cell's inherent physiological regulatory response to stimuli. Imposing a barrier between a highly metabolically active islet and its surrounding environment, however, commonly leads to impairment in nutrient delivery. Macroscale, avascular devices are typically plagued with slow delivery of nutrients and sluggish stimuli response times. Moving to the microscale, commonly in the form of beads, however, significantly improves surface to volume ratios, allowing for a more efficient exchange of hormones and

nutrients. While microencapsulation methods have been ongoing since the 1980s (32), progress has been hampered by quality control issues, such as inhomogeneity and impurities in the encapsulation materials, nonideal transplantation sites, instability of capsules, and large implantation volumes. Recent literature reports indicate advancement in addressing these issues, leading to improved function in diabetic animal models.

A more recent and much needed focus on the field of encapsulation has been on reassessing quality control issues, such as purity, stability, homogeneity, and porosity. Biomaterials used for encapsulation techniques should be well characterized, pharmaceutical grade, and verified as pyrogen and endotoxin free. Protocols for meeting these standards for common encapsulation materials, such as alginate, have recently been developed and will greatly assist in the improvement in consistency between scientific groups (8,9,14,39). Researchers, such as de Vos and his team, have also made significant advancements in characterizing and standardizing techniques for forming islet-containing microcapsules. Evaluation of critical parameters such as islet size, bead diameter, hormone and nutrient diffusivity, porosity, and cytokine protection using highly purified, endotoxin-free biomaterials have been conducted (6,7). Establishment of guidelines for generating capsules optimized for biocompatibility, immunoprotection, and islet function is critical for translation of encapsulation methods to clinical efficacy.

The peritoneal cavity has traditionally been used for the transplantation of encapsulated islet cells; however, the low oxygen tensions within the peritoneal cavity do not meet an islet's high oxygen demands (26). New locations that might meet the nutrient demands of encapsulated islets have recently been explored. In 2005, Toso et al. tested the compatibility of microcapsule composition and short-term immunosuppression in the intraportal vein (34). By injecting microcapsules built from five different alginate types, they were able to evaluate the effectiveness of the portal vein as an alternative to the peritoneal cavity for the transplantation of encapsulated cells. Their results showed that biocompatibility was high for barium-alginate microbeads and poor for polycation microcapsules. This study supports the portal vein as an alternative site for the transplantation of encapsulated islets; however, there are still issues with injecting encapsulated cells into the liver, such as possible occlusion. The omental pouch is emerging as a promising alternative site, given its desirable reconstructive characteristics, optimum arterial blood supply, and surgical accessibility (5). It also has been shown to be comparable, and in some cases superior, to the kidney capsule as a transplantation site for free islets (1,15). Kobayoshi et al. utilized this transplantation site to evaluate the ability of agarose encapsulated islets to restore normoglycemia in syngeneic NOD mice (16). In this study, the implanted agarose capsules functioned for up to 400 days without the use of immunosuppression, which is a significant improvement over previous results within the peritoneal cavity (17). Capillary formation near the capsules was observed upon biopsy, indicating that the omental pouch was conducive to angiogenesis at the engraftment site.

A novel approach to further enhance long-term survival of encapsulated islets is the combination of encapsulation techniques and short-term/low-dose immunosuppression or a targeted costimulation blockade regimen. Low-dose immunosuppression has been found to significantly increase engraftment and long-term function for microencapsulated islets in both allogeneic and xenogenic small-animal models (9,34). Furthermore, as illustrated Figure 2, the use of short-term immunosuppressive protocols can dramatically reduce capsular overgrowth, thereby increasing long-term efficacy (34). Early publications in rodents on the use of CTLA4-Ig, to block CD28/B7, and anti-CD154 mAb, as a means to inhibit CD40/CD40 ligand interactions, following the transplantation of microencapsulated xenogeneic islets illustrated the synergistic effects between encapsulation and targeted immunosuppression by significantly decreasing graft destruction (31). Recent publications on the use of a CD28-CD154 costimulation blockade regimen, specifically sirolimus and belatacept, in significantly delaying graft rejection of encapsulated porcine islets within rhesus macaques further illustrates the benefits of this combination strategy for improving graft survival and advances the feasibility of xenotransplantation in larger animal models (3,4).

Finally, recent advancements in the development of techniques for coating islets with nanoscale or conformal coatings have also shown incredible promise. By decreasing the capsule size by over 100-fold, problems of traditional capsules, such as graft volume, physiologic delay, and nutrient delivery, could be alleviated. Recent publications illustrate the numerous methods, biomaterials, and chemical protocols in which these coatings can be fabricated (22,24,25,33). The most common method of islet coating, PEGylation, in which the islet surface is covered with a layer of poly(ethylene) glycol molecules, has shown to result in decreased immune recognition, lymphocyte activation, and immune-mediated cytotoxicity in vitro (12,19,37). Combining PEGylation with low-dose immunosuppression, such as cyclosporine, has been shown to dramatically improve engraftment and long-term function of allogeneic rodent transplants, indicating that nanoencapsulation methods can serve to assist in immunocamouflaging implanted cells from the host long-term (18,20,38).

SUMMARY

The engineering of devices and encapsulation protocols for the development of a bioartificial pancreas has evolved significantly in recent years. As evident from the diverse examples presented, summarized in Figure 3, scientists are recognizing the importance of issues such as vascularization, mechanical protection, device design, biomaterial selection, and quality control. Efforts are now being made to overcome these common obstacles by developing novel biohybrid devices and encapsulation methods, and combining these techniques with agents such as targeted immunosuppressants and angiogenic factors. Furthermore, progress in the area of pancreas procurement, islet isolation, and islet quality control will assist in improving islet efficacy following transplantation. While the highly dynamic nature of cell-based transplants for the treatment of diabetes will continue to present challenges, the field is rapidly advancing on such challenges through the strengthening of collaborations between scientists from varying backgrounds, along with a reexamination of the critical issues within the field.

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