Published in final edited form as:

Adv Drug Deliv Rev. 2017 May 15; 114: 266–271. doi:10.1016/j.addr.2017.05.012.

Bio-synthetic materials for immunomodulation of islet transplants

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Abstract

Clinical islet transplantation is an effective therapy in restoring physiological glycemic control in type 1 diabetics. However, allogeneic islets derived from cadaveric sources elicit immune responses that result in acute and chronic islet destruction. To prevent immune destruction of islets, transplant recipients require lifelong delivery of immunosuppressive drugs, which are associated with debilitating side effects. Biomaterial-based strategies to eliminate the need for immunosuppressive drugs are an emerging therapy for improving islet transplantation. In this context, two main approaches have been used: 1) encapsulation of islets to prevent infiltration and contact of immune cells, and 2) local release of immunomodulatory molecules from biomaterial systems that suppress local immunity. Synthetic biomaterials provide excellent control over material properties, molecule presentation, and therapeutic release, and thus, are an emerging platform for immunomodulation to facilitate islet transplantation. This review highlights various synthetic biomaterial-based strategies for preventing immune rejection of islet allografts.

Graphical abstract

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1. Islet transplantation for treating type 1 diabetes

Type 1 diabetes (T1D) is an autoimmune disease characterized by specific destruction of insulin-producing β -cells in the pancreas, resulting in hyperglycemia and the accumulation of toxic acids in blood and urine. Individuals with T1D suffer from increased morbidity and mortality (1) and are at greater risk for other complications such as chronic kidney disease, cardiovascular disease, infections, and osteoporosis (2–4). An estimated 1.3 million adults and children in the US have T1D, and prevalence is expected to exceed 5 million by 2050 (5,6). Although T1D only accounts for 5–10% of the diabetic population, individuals with T1D incur disproportionately larger medical costs compared to type 2 diabetic patients (7). For example, in 2009, the annual institutional care costs for diabetic patients was \$10 billion, of which \$4.4 billion was spent on care for T1D patients (8). Thus, in addition to being one of the leading causes of morbidity and mortality, T1D represents a significant burden on US economic healthcare expenditures. To reduce medical costs and improve quality of life for individuals with T1D, there is a need for improving current treatment options. Whereas delivery of exogenous insulin, healthy dieting, and regular exercise are used to manage blood glucose levels, these treatments fail to maintain normoglycemic levels. Even with the use of manual injections of insulin or an insulin pump, individuals with T1D often live with chronic fear of hypoglycemia and suffer from serious secondary side effects such as hepatic impairment and renal dysfunction (9). Clinical islet transplantation, which involves the delivery of cadaveric allogeneic islets via infusion into the hepatic portal system, is the only treatment which provides physiological glycemic control (10,11). However, although initially effective in restoring normoglycemia in patients receiving transplants, the majority of these patients do not maintain long-term (> 5 years) insulin independence due to graft failure (12,13). These patients also require frequent delivery of immunosuppressive drugs, which are associated with severe negative side effects such as nephrotoxicity, neutropenia, fatigue, peripheral edema, and infections (14). Therefore, there is a significant need for engineering new therapies to reduce graft failure following clinical islet transplantation and eliminate the need for frequent administration of immunosuppressive drugs. Recently, biomaterial systems have emerged as effective tools for improving the engraftment and lifetime of cell-based therapies and for delivering bioactive molecules to modulate the local immune response to the graft. This review will first highlight the current limitations in clinical islet transplantation and inflammatory mechanisms that lead to destruction of islet allografts. Second, the use of different biomaterials for improving islet transplant engraftment and promoting long-term islet graft function will be discussed. We will focus on the use of synthetic materials to deliver exogenous bioactive molecules and cells that instruct local host immune cells to support tolerance to islet allografts.

2. Critical barriers in islet transplantation

The Edmonton protocol published in 2000 was a major breakthrough in clinical islet transplantation and significantly improved the frequency of patients that remained insulin independent by implementing a regimen of immunosuppressive drug therapy (15). However, several barriers limit the widespread use of this therapy. First, islet contact with the hepatic vasculature blood can trigger an instant blood mediated inflammatory reaction (IBMIR),

which results in complement activation, blood clot formation surrounding the islets and infiltration of leukocytes, ultimately culminating in the destruction of islet allografts (16). To address this limitation, alternative transplant sites such as subcutaneous, intramuscular, intraperitoneal, and omental sites have been explored as viable alternatives to the hepatic site. For more information on the benefits and pitfalls of extrahepatic transplant sites, we refer readers to other comprehensive reviews on the subject (17,18). Another limitation of clinical islet transplantation is islet anoikis (i.e. death of cells due to detachment from ECM), which is attributed to the destruction of cell-cell and cell-extracellular matrix (ECM) junctions during the islet isolation process (19). In addition to the destruction of ECM structures critical for islet survival, the islet isolation process also destroys native pancreatic vasculature. Although islets comprise only 1% of the pancreas, they consume 15% of the oxygen supplied from blood flow (20,21). Because of the high oxygen consumption required for islet survival, islet grafts maintained in a hypoxic environment fail within the first 2 weeks post-transplant (22,23). Therefore, new strategies for preventing islet anoikis and promoting revascularization of islet grafts are currently being explored. Discussion of these approaches are beyond the scope of the present paper, but excellent reviews provide information on engineered biomaterials that address these challenges (18,21,24). The final and perhaps most challenging limitation to address is host immune targeting and destruction of islet allografts in hepatic and extrahepatic transplant sites (25). Inflammation in response to the islets and material constructs that contain the islets leads to a decrease in islet function and destruction of the graft. This review will discuss synthetic biomaterial-based strategies for delivery of immunomodulatory molecules to prevent host immune rejection of allogeneic islet transplants.

2.1 Inflammatory cell response to islet allografts

Within hours following intraportal islet transplantation, IBMIR increases pro-inflammatory cytokines such as interleukins (IL)-6 and IL-8, interferon-inducible protein (IP)-10 and MCP-1 (26). This leads to rapid recruitment of innate immune cells such as monocytes, macrophages, and neutrophils near the transplanted islets and destruction of islet grafts (27,28). An additional factor in IBMIR is the activation of complement cascade, which leads to an increase in complement protein in the serum of islet transplant recipients (29). The activation of complement proteins C5a and C3a culminates in islet inflammation and death and the upregulation of adhesion molecules on the surface on endothelial cells and the recruitment and accumulation of leukocytes from blood. Allogeneic islet transplantation in extrahepatic sites significantly reduces graft failure from IBMIR. However, without frequent delivery of immunosuppressive drugs, chronic inflammation resulting from both innate and adaptive immune response mechanisms results in rejection of the islet graft. Thus, studies in both human and animal models of T1D have been performed to better understand the mechanisms governing immune cell targeting of islet allografts. For example, a recent report using DTR-CCR2 mice showed that depletion of CCR2⁺ monocytes with diphtheria toxin (DT) prolonged graft survival and normoglycemia in islet transplant recipients (30).

The islet isolation process activates inflammatory pathways in islets which lead to production of inflammatory cytokines. For example, islet secretion of IL-1 β exacerbates local inflammation which leads to the production of nitric oxide, which can inhibit insulin

secretion (31). Following recruitment of inflammatory cells, additional cytokines, such as tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), can further accelerate islet apoptosis (32). Strategies focused on systemic delivery of drugs and proteins that block the inflammatory activation from cytokines, such as IL-1R antagonists, show promise in improving islet graft survival (33). However, these therapies require frequent delivery and systemic administration of these agents remains challenging.

In addition to islet destruction from locally produced cytokines, antigens shed from the islet grafts trigger activation of adaptive immune cells, which results in rejection of transplants (34). The presentation of foreign peptides by major histocompatibility (MHC) on host antigen presenting cells (APCs) activates adaptive immune response involving CD4⁺ and CD8⁺ T cells. This process is outlined in Figure 1 in the following steps: (1) maturation of antigen-presenting cells, such as dendritic cells (DCs), (2) migration of DCs to draining lymph nodes, (3) education and expansion of alloreactive T-cells by DCs, and (4) migration of alloreactive T-cells to the transplant site and cytotoxic destruction of islets (35). The autoimmune response also plays a significant role in the rejection of islet allografts, whereby the transplanted islets activate humoral responses (29). In fact, 7–8% of islet transplant recipients may develop type 1 diabetes recurrence that is not mitigated with immunosuppression (36).

To suppress immune rejection of islet grafts, the Edmonton Protocol relies on frequent systemic delivery of anti-inflammatory drugs (rapamycin – inhibits mTOR pathway and IL-2 production; tacrolimus – inhibits IL-2 production) and a therapeutic anti-CD25 monoclonal antibody, which augments the generation and function of regulatory T cells (Tregs) (15). To circumvent the negative side-effects associated with systemic delivery of immunosuppressant drugs, alternative strategies, such as local delivery of anti-inflammatory drugs and immunomodulatory molecules, are being explored. For example, systemic delivery of cytotoxic T lymphocyte antigen fusion protein (CTLA4-IgG), which binds to CD80 or CD86 on the surface of antigen presenting cells to deactivate them, has been effective in reducing allo- and autoimmune responses to islet transplants and has improved graft lifetimes (37,38). In another example, Yolcu et al. showed that tethering of chimeric Fas ligand-streptavidin (FasL-SA) to the surface of islets transplanted under the kidney capsule prolonged graft survival compared to unmodified islets. It is well appreciated that Tregs are instrumental in maintaining immune homeostasis, peripheral tolerance to foreign antigens, and even self-tolerance (39,40). Tregs, which are identified by expression of CD25 and the transcription factor forkhead box P3 (FoxP3), provide immune suppression by outcompeting effector T cells (Teffs) for interaction with DCs, modulating the APC function, and producing anti-inflammatory cytokines such as IL-10. Therefore, strategies to induce generation of Tregs around the islet graft are being pursued. Since natural clearance of apoptotic cells in the circulation is important in maintaining antigen tolerance, one such study exploited this process to establish immune tolerance. Specifically, the authors delivered erythrocyte-binding antigens to decrease the generation of activated CD4 and CD8 T cells and promote generation of Tregs in the draining lymph nodes and in the spleen (41,42). Importantly, the erythrocyte-binding antigen protected mice from developing T1D by preventing the activation of autoreactive T cells.

3. Biosynthetic materials for islet delivery

Synthetic biomaterials are an attractive platform for protein and cell delivery in regenerative medicine applications. Compared to naturally derived materials, synthetic biomaterials offer better reproducibility and control of mechanical properties, degradation rate, shape, and chemical composition. Specifically, biosynthetic materials are used to: conformally coat islets in order to establish an immunoprotective barrier (43,44), present basement membrane proteins to promote islet survival (45–47), deliver factors to facilitate vascularization of islet grafts (48–50), and deliver bioactive molecules that suppress immune targeting of islet allografts (51) (Figure 2). A wide range of synthetic polymeric materials have been applied to islet transplantation (52,53). The most commonly used synthetic materials for these applications include poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), and derivatives of these materials.

3.1 Islet microencapsulation

Nearly forty years ago, Lim and Sun demonstrated prolonged survival and function of islets encapsulated within alginate hydrogel microparticles (54). Diabetic rats receiving unencapsulated islets within the intraperitoneal cavity maintained normoglycemia for up to 1 week, while encapsulated islets maintained normoglycemia for 2–3 weeks without immunosuppression. Since this study, islet microencapsulation has considerable attention as a therapeutic strategy for preventing immune destruction of islet allo- and xenografts (55,56). In contrast to unencapsulated islets, encapsulated islets are mainly delivered to extrahepatic transplantation sites such as the omentum, intraperitoneal cavity, and subcutaneous space (57,58). Therefore, it is important to select a biomaterial that serves to protect transplants from allo-rejection and autoimmune destruction as well as permit the exchange of oxygen, glucose, insulin, and nutrients critical for islet survival. The encapsulating material needs to prevent the accumulation of immune cells and fibrosis that ultimately limit mass transport of nutrients to islets and lead to islet death. Macroencapsulating devices such as the VC-01™ from ViaCyte have proven effective in limiting the accumulation of immune cells, while allowing the establishment of a local vascular bed. There has been significant progress using natural materials such as alginate to encapsulate islets or stem cell derived β -cells to reverse hyperglycemia. Notably, delivery of stem cell-derived β -cells that are encapsulated within a chemically modified alginate restores normoglycemia in diabetic mice for 90 days (59). Here we will focus on the use of synthetic biomaterials for islet microencapsulation and treatment of T1D. For more information on the use of alginate or other natural biomaterials we refer readers to the following reviews (60,61).

PEG is one of the most commonly used synthetic biomaterials for islet encapsulation. The Hubbell group tested the biocompatibility of tetra-acrylated PEG to encapsulate islets and found no difference in the viability and function of encapsulated islets compared to free islets *in vitro* (43). In a follow-up study, PEG diacrylate was used to encapsulate porcine islets and the function of islets was evaluated *in vitro* and *in vivo* (62). Encapsulated porcine islets restored normoglycemia in immunocompromised diabetic mice for more than 100 days. In an immune competent rat model, encapsulated porcine islets maintained viability

and insulin production in the intraperitoneal fat pads for 30 days. Other groups have used PEG to encapsulate and immunoisolate islets using various techniques. The primary focus of these techniques is to achieve thin conformational coating of PEG on the surface of islets to improve the exchange of nutrients and increase islet viability. In one application, a PEG-lipid structure assembled into a thin layer surrounding islets in suspension (63), and these coatings reduced the instant blood-mediated inflammatory reaction to transplanted cells (64). In another strategy, layer-by-layer assembly of poly(L-lysine)-*g*-poly(ethylene glycol) (biotin) (PPB) and streptavidin (SA) is applied to generate a thin multilayer film encapsulating islets (44). Similarly, a PEGylated silicon nanopore membrane to encapsulate islets protects islets from cytokine induced inflammation and destruction *in vitro* (65). Recently, PEGylation alone provided modest immunosuppression in an allogeneic transplant model (66). Combined with regular delivery of immunosuppressive drugs, mice that received PEGylated islets exhibited long-term normoglycemia.

Microfluidic devices have become an attractive method for achieving high throughput encapsulation of cells within biomaterials (67,68). Microfluidics-based polymerization has been developed to generate islets encapsulated within PEG microgels (69). Microencapsulated islets produced insulin in response to glucose and remained viable during *in vitro* culture for at least 8 days, but the *in vivo* function of these islets has yet to be determined. Using a microfluidic device to encapsulate islets in a conformational coating of PEG (70), a curative dose of islets could be delivered within the renal subcapsular space. Both bare islets and microencapsulated islets restored normoglycemia for over 100 days after transplantation into syngeneic diabetic mice. The capacity of this method of conformational coating in protecting islets from auto- and allo-rejection has yet to be explored.

Whereas extensive research has been performed with using PLGA microspheres to control release of therapeutic drugs and proteins, only recently has PLGA been used for cell microencapsulation. This is in large part due to the challenges associated with PLGA, specifically the pH drop that occurs during degradation, which can result in aggregation of loaded proteins and elicit an immune response (71,72). Porcine islets encapsulated in PLGA microspheres and transplanted into the abdominal cavity of diabetic rats reduced blood glucose levels compared to control subjects (73), however the animals failed to return to normoglycemia.

Synthetic material encapsulation prevents the direct recognition of donor islet MHCs and peptides on the surface by host T cells. However, antigens shed by encapsulated cells can penetrate the material and interact with host T cells in the local microenvironment. Although the exact effect of indirect antigen presentation in contributing to islet destruction is still unclear, strategies focused on local immunomodulation of the immune response are being explored(51,74,75).

3.2 Delivery and presentation of immunomodulatory molecules

Whereas many biomaterial-based strategies for islet transplantation involve encapsulation of islets to confer protection from immune cells, degradable and porous scaffolds encourage the infiltration of cells to promote engraftment and vascularization of islets. Therefore,

bioactive proteins and drugs that protect islet allografts from immune destruction are needed for scaffolds that permit cell infiltration. Synthetic biomaterials have proven to be efficient platforms for delivering immunomodulatory proteins and drugs that prevent rejection of islet allografts. To overcome the coagulation cascade that results from IBMIR following hepatic transplantation, strategies to co-deliver anticoagulants have with encapsulated islets have been explored. For example, Staudinger ligation chemistry has been applied to link thrombomodulin on the surface of PEG encapsulated islets (76). PEGylation and presentation of thrombomodulin or urokinase does not negatively affect islet viability or insulin release (77). While the *in vitro* data from these studies suggest that the anticoagulants retain bioactivity, there are currently no reports demonstrating the benefit of this therapy *in vivo*.

Biomaterial-based delivery of anti-inflammatory molecules with islets has shown promise as an effective therapy to prevent immune targeting of islet allografts and eliminate the need for lifelong immunosuppression. The Shea group has reported that syngeneic islets within a PLGA scaffold restore normoglycemia following transplantation within abdominal fat pads (78). In a subsequent study, allogeneic islets and Tregs were seeded within the PLGA scaffold to suppress the host immune response and prevent islet destruction (79). Compared to diabetic mice that received Tregs systemically, mice that received PLGA scaffolds containing Tregs maintained normoglycemia beyond 10 days, the average rejection time-period for rejection of islets within PLGA scaffolds. In addition to suppressing activation of islet-specific T cells and conferring local tolerance to islets, PLGA scaffolds containing Tregs induced systemic tolerance. Allogeneic islets transplanted within the kidney capsule remained viable and maintained normoglycemia even after PLGA scaffolds containing Tregs were excised from the fat pads. In addition to immunomodulation using Tregs, recent efforts have focused on engineering PLGA scaffolds with controlled release of TGF- β 1 (51). Scaffolds containing TGF- β 1 restored normoglycemia and prolonged survival of allogeneic islets compared to PLGA scaffolds without TGF- β 1. This result was attributed to a decrease in the recruitment of macrophages, dendritic cells, and natural killer cells. However, despite improvement in the survival time of islet allografts and overall decrease in inflammation within the PLGA grafts, all mice became hyperglycemic by 28 days post-transplantation.

In addition to PLGA-based strategies, PEG biomaterials have recently been used for immunomodulation of islet transplants. Islets encapsulated within PEG containing a crosslinked hemoglobin (Hb-C) scavenge reactive oxygen species that are generated by macrophages during the immune response (80). In contrast to islets encapsulated without Hb-C, islets encapsulated with Hb-C were protected from destruction when cultured with nitric oxide donors *in vitro*. In another strategy, PEG hydrogels presenting peptides which sequester the pro-inflammatory cytokines TNF α and MCP-1 (81,82). Cells cultured within PEG hydrogels with the sequestering peptide remain viable when cultured in the presence of TNF α . The capacity of this system to improve islet transplantation has yet to be determined. PEG biomaterials have also been used to locally deliver drugs that suppress the immune response. Trapping rapamycin using PEG around alginate microspheres containing porcine islets decreased the level of fibrosis surrounding the alginate microspheres (83).

4. Concluding remarks

Although still in the early stage of development, synthetic biomaterials have proven beneficial in improving islet transplantation via encapsulation and delivery of immunomodulatory molecules. A combined therapeutic approach involving both encapsulation of islets and presentation of immunomodulatory molecules will ultimately result in long-term maintenance of normoglycemia in T1D patients. In fact, to improve the long-term survival of transplanted islets, a degradable encapsulating scaffold combined with local immunomodulation would serve to facilitate vascularization and engraftment of islets while preventing immune cell destruction. While it remains unclear as to which immunomodulatory factor best prolongs the survival of islet allografts, studies suggest that motifs which directly promote the generation of Tregs also improve islet transplantation. In fact, the combination of multiple immunomodulatory factors presented on the biomaterial or released from the biomaterial may work in synergy to support local immune tolerance to allogeneic islets that provide long-term normoglycemia.

Acknowledgments

This work was funded by the U.S. National Institutes of Health (R21 EB020107) and the Juvenile Diabetes Research Foundation (2-SRA-2014-287-Q-R).

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Figure 1.

(a) Donor antigen is shed from islets and taken up via receptor mediated endocytosis by antigen presenting cells such as dendritic cells. Internalized antigen is processed and peptide fragments are presented on the surface of dendritic cells via major histocompatibility molecules, (b) Dendritic cells then migrate to draining lymph node and present donor peptide to T-cells. (c) T-cells that interact with peptide become activated and upregulate cytokine and cytokine receptors that promote expansion, (d) Activated T-cells migrate to donor peptide source and release cytokines that promote islet destruction.

Figure 2.

Two primary applications of biomaterials for protecting islet isolation include microencapsulation and immunomodulation. Microencapsulation involves creating a biomaterial barrier that permits the exchange of insulin, glucose, oxygen, and other nutrients, while at the same time preventing infiltration of immune cells and antibodies. Immunomodulation involves controlled local delivery of immunomodulatory factors that instruct the local immune environment to adopt a tolerogenic phenotype, such as the generation of Tregs and deletion of Teffs.