HHS Public Access

Author manuscript

Curr Diabetes Rev. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Curr Diabetes Rev. 2015 ; 11(3): 163–169.

Engineering Biomimetic Materials for Islet Transplantation

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Abstract

A closed-loop system that provides both the sensing of glucose and the appropriate dosage of insulin could dramatically improve treatment options for insulin-dependent diabetics. The intrahepatic implantation of allogeneic islets has the potential to provide this intimate control, by transplanting the very cells that have this inherent sensing and secretion capacity. Limiting islet transplantation, however, is the significant loss and dysfunction of islets following implantation, due to the poor engraftment environment and significant immunological attack. In this review, we outline approaches that seek to address these challenges via engineering biomimetic materials. These materials can serve to mimic natural processes that work toward improving engraftment, minimizing inflammation, and directing immunological responses. Biomimetic materials can serve to house cells, recapitulate native microenvironments, release therapeutic agents in a physiological manner, and/or present agents to direct cells towards desired responses. By integrating these approaches, superior platforms capable of improving long-term engraftment and acceptance of transplanted islets are on the horizon.

Keywords

biomaterials; scaffolds; diabetes; encapsulation; inflammation; anoikis; immunomodulation

INTRODUCTION

Type 1 diabetes mellitus is classified as an autoimmune disease, owing to the selective destruction of the beta cells within the pancreatic islet [1]. Patients exhibit a progressive loss of insulin production and secretion with concurrent erratic blood glucose levels. Diagnosis of diabetes has increased in recent years, with a rise in documented cases from 1.48 to 1.93 cases per 100,000 between 2001 and 2009 [2].

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Conflict of Interest

CLS has stock options in Converge Biotech Inc. (Miami, FL).

Currently, the therapeutic regime for type 1 diabetics includes exogenous insulin delivery [3]. The concept of a “closed loop” glucose sensor-insulin secretion system has moved closer to clinical translation due to recent engineering advancements; however, significant obstacles are still present, including glucose sensor accuracy and lag time, as well as insulin delivery methods and robust controllers. Islet transplantation has progressed from intellectual curiosity to realistic therapy over the past decade, as it has the potential to provide intimate and innate blood glucose control.

The current Clinical Islet Transplantation (CIT) protocol involves the intrahepatic injection of pancreatic islets, where they lodge in the liver microvasculature. While CIT has shown tremendous promise, the long-term function of these grafts has not proven to be adequate [4, 5]. Immediately following intraportal islet infusion, a large percentage of the islets are lost (> 60%). This loss has been observed in both allogeneic and syngeneic models, indicating that the mechanisms of cell death are not solely dependent on specific immune responses [6, 7]. Through these studies, researchers have identified critical issues that hamper islet survival, both in the short and long term. In the initial engraftment period, challenges include islet anoikis, delayed revascularization, and the host inflammatory response. For long-term engraftment, challenges include host innate and antigen-specific adaptive immune responses. Recent approaches seek to mitigate these issues by engineering *biomimetic materials* (i.e., materials capable of mimicking or directing a desired biological mechanism) that are capable of replicating the native islet environment or directing desirable host responses, as summarized in Table 1.

PALIATINGISLET ANOIKIS

In their native environment, islets are embedded within a niche of extracellular matrix (ECM) composed of basement membrane proteins, predominated by collagen type IV, laminin, and fibronectin [8]. These dynamic three-dimensional structures not only play an instructive role in islet survival, function, and proliferation, but also serve to regulate inflammatory and immunological pathways [9]. Isolation procedures disrupt this microenvironment, resulting in islet anoikis (i.e., cellular homelessness that induces activation of pro-apoptotic pathways) [8]. Further, homotypic and heterotypic cell-cell interactions within the pancreatic islet are critical for the maintenance of appropriate function [10]. Therefore, reestablishment of the three-dimensional ECM and maintenance of the appropriate cell-cell interactions are critical in engineering a functional *ex vivo* niche.

Two of the most common biomaterials used for islet transplantation are alginate and poly(ethylene glycol) (PEG) hydrogels [11–13]. While easy to use and stable, they are fundamentally inert biomaterials and do not dynamically interact with the encapsulating cells. While this approach might be desirable for some applications, the loss of instructive interactions between the material and the embedded cells can result in accreting dysfunction or apoptosis via activation of anoikis. This phenomenon was illustrated by Lin et al. [14], whereby low beta cell seeding within PEG hydrogels resulted in dysfunction and loss of cells, while high loading densities produced favorable cell responses. This correlation was attributed to modulation of cell-cell interactions. While high cell seeding can lead to more favorable cell-cell interactions, these loading densities may not be optimal for nutrient

delivery. Biomimetic materials can recapitulate these cell-cell interactions without these limitations. For example, the incorporation of the cell-cell receptors ephrin-As and EphAs into PEG hydrogels resulted in improved beta cell survival and function, when compared to unfunctionalized gels [14, 15]. ECM components, such as fibronectin, collagen, and growth factors, have also been incorporated within biomaterials to promote beta cell stability. For example, insulinoma cells photoencapsulated in PEG gels containing collagen IV and laminin demonstrated increased insulin secretion, when compared to gels without said components [16]. It has also been shown that cell-cell and cell-ECM interactions can be recaptitulated using decellularized pancreatic matrix components absorbed onto microbeads [17]. As an alternative approach, anti-apoptotic agents, such as the hormone glucagon-like peptide 1 (GLP-1) have demonstrated efficacy in promoting islet survival when tethered to a biomaterial [18].

While contact-dependent signaling promotes survival, islets encapsulated within polymers are dependent on simple diffusion of oxygen, nutrients, and waste, sometimes over large distances. With this in mind, macroporous scaffolds, which permit host cell infiltration, are an effective platform; permitting the graft to be architecturally integrated within the host. In addition to the incorporation of ECM components such as collagen IV [16], poly(lactic-co-glycolic acid) (PLGA) macroporous scaffolds have also been designed to actively promote islet engraftment *via* the sequential release of insulin-like growth factor (IGF) and transforming growth factor beta 1 (TGF-β1)into the local environment [19, 20]. The capacity of these trophic factor-loaded scaffolds to facilitate islet function and survival *in vivo* remains to be explored. Overall, materials that mimic the islet niche, either through the presentation of ECM mimetics or the secretion of desirable engraftment factors, can provide a controlled approach for directing the graft microenvironment toward favoring islet survival and function.

ENHANCING ISLET REVASCULARIZATION

Pancreatic islets require an extraordinary degree of vascularization, which is essential to support their oxygen demand and provide optimal glucose-responsive insulin secretion. Unlike whole organ pancreas transplantation where perfusion is quickly restored upon vessel anastomosis, the islet isolation process strips the native vascular architecture, resulting in an extended period of neovascularization following implantation. Therefore, an appreciable proportion of islets suffer from ischemic injury in the immediate post-transplant phase. Further, if islets are encapsulated for immunoprotection, complete islet revascularization is not feasible. As such, engineering sites with optimal vascularization are crucial to abating islet hypoxia and providing superior glycemic responsiveness.

Various approaches have been employed to promote a rich vascular network following islet transplantation. The use of a scaffold to guide a vascular network is one approach. For example, a decellularized pancreas serves as a simple, yet functional, biomimetic organ platform for transplantation, as vascular channels are preserved within the existing natural construction of the ECM. Islets seeded within these scaffolds exhibit physiological insulin secretion under basal and high glucose conditions [21, 22]. As an alternative approach, the transplant site could be prepared prior to islet implantation to alleviate the exposure of

sensitive islets to the inflammatory and hypoxic environment that typically accompanies neovascularization [23–25].

While it has long been known that angiogenic growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and endothelial growth factor (EGF), can significantly improve vascularization, the simple delivery of these factors to the local microenvironment results in the loss of spatial and temporal gradients, leading to dysfunctional vessel formation. The incorporation of "helper" cells, such as endothelial or mesenchymal cells, can promote stable and physiological neovascularization; however, the additional nutritional burden of these cells on the transplant site during early engraftment can outweigh their long-term benefits.

Biomimetic materials strive to mimic the native temporal and spatial controlled presentation of these factors via tethering to dynamic materials. Thus, as the material interacts with the host cells, release of the angiogenic factors provides instruction and direction to the vascular sprout. On the synthetic material side, nanofibers composed of heparin and heparin binding peptide amphiphiles have been engineered to present desired growth factors [26]. These nanostructures retain localized VEGF and FGF2, thereby facilitating revascularization and improving engraftment. Another approach links degradable PEG hydrogel with VEGF and hepatocyte growth factor (HGF), resulting in increased vessel density [27]. Alternatively, native binding domains and natural materials can be used for the same purpose. For example, we studied the use of fibrin gel, linked to a fibronectin (FN) fragment capable of presenting both a growth factor and major integrin binding domain, and observed the synergy of this presentation on islet engraftment. Scaffolds containing fibrin/FN/PDGF gels exhibited improved engraftment efficacy in syngeneic transplant models [28]. The use of native ECM proteins can promote islet survival and vascularization. For instance, collagen matrices containing chondroitin-6 sulfate, chitosan, and laminin demonstrated enhanced vascularization post-transplantation [29]. Alternative approaches explored the use of the unique proangiogenic factor sphingosine-1-phosphate (S1P) prodrug FTY720. FTY720 is typically used to sequester lymphocytes in secondary lymphoid tissue [30]. While systemic delivery inhibits angiogenesis, the local delivery of FTY720, using nanofiber scaffolds, was shown to stimulate neovascaularization [31,32]. Overall, highly promising biomimetic materials capable of recapitulating native mechanisms for guided and controlled neovascularization are poised to make a significant impact in the field of islet transplantation.

On a different note, while pro-vascularization approaches improve oxygen delivery in the long-term, the development of a functional vascular bed takes, at minimum, several days. In the interim, islet necrosis occurs due to severe hypoxia. To alleviate this loss, investigators are exploring the use of *in situ* oxygenation [33]. Our group has developed a hydrolytically reactive, oxygen generating, biomaterial, based on the encapsulation of solid calcium peroxide within polydimethylsiloxane (PDMS) [34]. *In vitro* testing exhibited prevention of hypoxia-induced cell death and insulin secretion dysfunction, when these materials were used. Alternatively, the use of an oxygen chamber adjacent to the encapsulated islets has shown significant promise in small and large animal studies [35–37]. As a complementary approach, oxygen delivery platforms can be combined with proangiogenic growth factors.

For example, Shimoda *et al.* incorporated a VEGF vector into lipid-stabilized micro bubbles, which also contained perfluorocarbon gas [38]. This technology facilitated revascularization of islets transplanted into the liver. Overall, ensuring appropriate oxygenation of the islet transplant is a critical component for success, particularly for extra hepatic sites. Current biomimetic approaches have shown great potential in achieving this goal.

DAMPENINGINFLAMMATORY PROCESSES

Transplanted islets incite two different inflammatory pathways: instant blood-mediated inflammatory reaction (IBMIR), an inflammatory and thrombotic reaction specific to islets; and generalized surgical inflammation, a tissue injury reaction associated with trauma. Following intrahepatic islet transplantation, islets are in direct contact with blood. This contact instigates IBMIR, which involves platelet adherence to the islet and activation of coagulation and complement cascades [39]. This response is believed to contribute to significant islet loss immediately after infusion, resulting in decreased clinical efficacy [40]. In addition, these inflammatory elements act as chemo attractants for neutrophils and monocytes, leading to islet infiltration and attack [41]. Overall, these inflammatory events brew a highly toxic islet microenvironment.

Through extensive *in vitro* and clinical trial studies, it has been identified that tissue factor (TF) present on the surface of islets is a strong contributor to IBMIR. Traditionally, clinical IBMIR has been ameliorated with heparin, dextran sulfate, and a complement inhibitor (SCA1); however, systemic administration of these agents can lead to bleeding complications, while demonstrating only a marginal impact on ameliorating IBMIR. More targeted approaches to block TF on the cell surface, such as the use of antibodies, have resulted in dampened inflammatory responses [42], but delivery of these antibodies has proven to be complex.

Biomaterials could provide a more benign and localized platform to mask cell surface factors that are associated with IBMIR activation. Simple polymer coatings using materials such as alginate, PEG-lipid, and other PEG derivative surface-modifications have been shown to rescue islets from early-phase IBMIR-mediated destruction [43, 44]. The further functionalization of coatings to engineer biomimetic platforms, such as the co-immobilization of motifs, can serve to actively inhibit complement activation and serve as anticoagulants. For example, Cabric et al. used biotin/strepavidin to tether heparin to islet surfaces, which resulted in attenuated levels of thrombin, antithrombin, and complement C3a [45]. Thrombomodulin, a transmembrane protein that binds thrombin and inhibits its ability to cleave fibrinogen and activate factor V, factor VIII, or platelets, has been tethered to PEGylated islets [46], layer-by-layer avidin/biotin coatings [47], and lipid bi-layers [48]. These approaches have demonstrated decreased activation of coagulation pathways, marked conversion of the anticoagulant activated protein C, and decreased intraportal fibrin formation and neutrophil infiltration. Islet surfaces have also been coated with PEG-lipid and further modified with immobilized urokinase, a fibrinolytic enzyme [49]. These islets experienced reduced ischemia, cell injury, and blood coagulation. As such, coating strategies designed to actively modulate the islet-blood interface can locally mitigate IBMIR.

In addition to IBMIR, generalized inflammatory pathways are specifically detrimental to islet survival. For example, interleukin-1 (IL-1), produced by the pancreatic islets, not only drives inflammatory processes but also leads to the production of nitric oxide, which can inhibit insulin secretion [50]. The release of additional cytokines, such as IL-1β, IL-6, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), can further accelerate islet damage and destruction [51]. While blockage of IL-1 through an IL-1 receptor antagonist (IL-1Ra) produces anti-inflammatory activity [52], the systemic delivery of these agents is challenging. A biomimetic strategy used PEG hydrogel tethered with IL-1 receptor inhibitor peptide, which reduced beta cell death following IL-1β, TNF-α and IFN-γ exposure [53]. Further investigations into the relative contributions of these factors in impairing islet function, and engineering biomaterials that aim to attenuate these inflammatory reactions, are warranted.

MODULATING ADAPTIVE IMMUNITY

Following islet transplantation, as with other allogeneic organ transplants, variation in human leukocyte antigen (HLA) activates an adaptive immune response involving both CD4+ and CD8+ T cells, which result in targeted host cell attack. Unique to type 1 diabetes is the role of autoimmunity, whereby the transplanted islets can also activate humoral responses. As such, current islet allograft recipients must rely on systemic immunosuppressant or anti-rejection therapy. While adjustments to the dosage and drugs used in the immunosuppressive regimen have been made since the original Edmonton protocol [54, 55], challenges remain in mitigating side effects, maintaining patient compliance, and achieving full protection of the islet graft.

An attractive alternative to systemic immunosuppression is the polymeric encapsulation of islets to mask direct antigen presentation. Microencapsulation was firstly described in the 1960s by Chang et al. [56]. Since then, various permutations and geometries have been employed, from the macro to nano scale. Recent clinical publications demonstrate some promises in polymeric encapsulation for protecting islets from host immune attack. For example, recipients of microencapsulated allogeneic islets exhibited reduced HbA1c levels and exogenous insulin requirements, without the detection of alloantibodies [57]. Further, Ludwig et al. implanted a macroscale encapsulation device, supplemented with oxygen that offered protection of the graft with no changes in islet autoantibody and donor alloantibody [58]. While limited blood glucose control was observed, this was likely due to an inadequate number of transplanted islets. On the research side, new polymers and encapsulation methods are being explored for the fabrication of ultrathin coatings. For example, islets have been encapsulated within PEG-based conformal coatings using a microfluidic platform [59]. Alternatively, the layer-by-layer deposition of polymers, either via electrostatic interactions [60], hydrogen bonding [61], or covalent linkages [62], has shown promise, with some approaches providing immunoprotection in allograft rodent models [63].

While polymeric encapsulation may serve to block direct antigen presentation (i.e. the direct recognition of donor MHCs and peptides on the surface by host T cells), indirect antigen presentation (i.e. the presentation of shed antigens by host antigen presenting cells (APC) to host T cells in a self-restricted manner) is likely still activated, as coatings permit shed

antigen release into the local microenvironment. This immune activation is expected to be further exacerbated when xenogeneic islets are employed, as the degree of foreign antigens is further elevated. While the exact role of indirect antigen presentation in graft loss or dysfunction is still unclear, approaches seeking to direct host immune responses toward tolerogenic pathways could further enhance graft longevity.

Manipulating the presence of regulatory T cells (Tregs) is one of the primary approaches used to direct immune cell responses toward acceptance of foreign cells. Tregs, a crucial subset of T cells, modulate innate and adaptive immunity, thereby helping to maintain balance in effector responses. The generation of Tregs tolerant to islet antigens could lead to a local (and possibly systemic) environment that favors long-term islet acceptance. The co-transplantation of islets with *ex vivo* expanded Tregs demonstrated delayed CD34+ stem cell-mediated rejection of islet transplants, via decreased macrophages and neutrophil recruitment to the islet allograft and inhibition of cytokine production of IFN-γ by Th1 T cells [64, 65]. While polyclonal Tregs induce delays in rejection, this approach is inefficient; requiring large numbers to achieve beneficial effects [66]. Alternatively, alloantigen-specific Tregs have shown enhanced potency, with establishment of long-term graft tolerance via selective suppression of Th1 cells [67]. These results suggest that antigen-specific Tregs may be the most effective population to employ for prevention of allograft rejection [66].

While the use of *ex vivo* expanded Tregs has potential, ensuring stable engraftment of these cells is an appreciable challenge, as substantial Treg loss is commonly observed following transplantation [68]. The generation of Tregs at the site of implantation may be a more stable approach, whereby T cell recruited to the islet graft can be converted to Tregs by the local microenvironment. Recent efforts have sought to engineer this via a biomimetic materials approach through two main tactics: 1) the local release of immunomodulatory agents; and 2) the surface presentation of immunomodulatory signals.

The local release of soluble immunosuppressive factors holds great interest in the field of allograft transplantation, as local delivery reduces the cost and side effects typically associated with systemic delivery, while still retaining potency. Tailoring the local delivery of these soluble agents, however, can be a challenging task. The material selected should be customized to the desired agent to ensure compatibility and the desired kinetic release, while not inciting an immune response. Some of the most common materials employed for local drug delivery are poly (D,L-lactic) acid (PLA) and poly (D,L-lactic glycolic acid) PLGA. These materials have been doped with steroids, such as the corticosteroid loteprednol etabonate (LE) or dexamethasone, to build a delivery system that minimizes systemic side effects while maximizing local efficacy [69]. In addition, these formulations were found to prolong allograft survival by giving rise to a local immunosuppressive environment [70]. Alternatively, these materials have been used to deliver signals for Treg induction, e.g. PLGA microspheres releasingIL-2, TGF-β1, and rapamycin [71]. It is postulated that local release of these agents in the context of an allograft can direct antigen-specific Treg generation. Other biomaterial platforms are emerging that may provide more dynamic release characteristics. For example, tacrolimus was locally delivered using the self-assembled amphiphiletriglycerol monostearate (TGMS), with release modulated via

enzymatic degradation *in vivo*. This material resulted in long-term acceptance of a vascular composite allograft in a hind limb model [72].

In lieu of local soluble release, the presentation of selected agents on a material surface can serve to direct host immune cell responses. These agents could be tethered to materials co-transplanted with the islets, linked to the cell surface via reactive polymers, or incorporated within the polymeric material used to encapsulate the islets. The most common agents selected are those capable of directing T cell responses, particularly by the manipulation of the second signal. In one approach, functionalized FasL, termed SA-FasL, was linked to a cell surface using strepavidin-biotin binding [73]. The resulting SA-FasL coated islets demonstrated long-term graft acceptance, which was attributed to the elimination of alloreactive T cells and a subsequent increase in Tregs. While previous reports demonstrated that FasL overexpression by islets failed to protect allogeneic hosts, this was likely due to the form of expression [74, 75]. When membrane-bound FasL is cleaved by metalloproteinases and becomes soluble, it has been found to activate inflammatory responses and promote neutrophil recruitment [73]. In contrast, the membrane-bound form of FasL induces apoptosis and eliminates the self-reactive T cells [76]. As such, the presentation of these immunomodulatory proteins is a significant variable to consider when designing these materials.

Immunomodulatory motifs can also be added to encapsulating hydrogels, whereby direct antigen presentation is blocked by the encapsulating material while motifs can modulate indirectly activated immune cells. As an illustration, Hume et al. modified TGF-β1 and IL-10 by thiolization and linked this to a PEG hydrogel [77]. The resulting polymer surface was found to decrease activation of dendritic cells. The sufficiency of this immunosuppressive approach to protect islet survival against allogeneic rejection *in vivo* would be of interest for future studies.

Finally, a scheme for tolerance induction that has shown strong potential is one that exploited the natural clearance of apoptotic cells to induce antigen-specific tolerance. This was firstly demonstrated using ECDI-fixed donor splenocytes, which resulted in the long-term acceptance of allogeneic islets in a rodent model [78]. This approach was translated to a strictly biomimetic platform using both material microparticles and polymer linkers, which presented peptides to induce antigen-specific tolerance in a mouse model of autoimmune encephalomyelitis [79–81]. Subsequently, this was applied to islet transplantation, whereby donor antigen-coupled biodegradable particles using donor spleen lysates were administered to induce tolerance in recipient animals [82]. Subsequent transplantation of matched islets resulted in allograft protection for over 250 days. Overall, these platforms could be used for directing tolerogenic responses, which would serve to not only address generalized allograft immunity, but possibly autoimmune responses.

NEW DIRECTIONS

Developing biomimetic materials for islet transplantation, while still in early stages of development, has the potential to emerge as a successful strategy in constructing a functional and stable endocrine organ. ECM biomimetics rescues islets from anoikis, while

oxygen-generating and angiogenic materials promote revascularization of the voracious islet. Encapsulation can provide long-term engraftment, while the local secretion or immobilization of immunomodulatory motifs endeavors to attenuate and direct inate and adaptive immune responses. Combining these platforms would ultimately result in a physiological-like endocrine pancreas, engrafted within an ectopic site, without systemic immunosuppressive therapy. Further, advancements made in biomimetic materials for islet transplantation could easily translate to the field of organ transplantation and tissue engineering as a whole.

Acknowledgments

The authors are currently supported by the National Institutes of Health (R01DK100654 and UC4DK104209) and the Juvenile Diabetes Research Foundation – Helmsley Trust Center Grant (17-2012-361 and 17-2013-303).

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Table 1

A summary of problems and biomimetic approaches outlined in this review.

Problem	Biomimetic Approach
Anoikis	Mimicry of cell-cell interactions on benign encapsulation polymers
	Incorporation of ECM mimetics, anti-apoptotic components, and trophic factors
Vascularization	Use of decellularized organs, such as the pancreas
	Scaffold-, nanofiber-based delivery of ECM components and angiogenic growth factors
	In situ oxygen generation
Inflammation	Surface tethering of native anticoagulant or anti-inflammatory agents
	Local release of anti-inflammatory agents
Adaptive immunity	Cellular encapsulation within benign polymers
	Local delivery of immunosuppressive factors via biomaterials
	Immunomodulatory motifs tethered to encapsulating polymers