


Multifunctional Islet Transplantation Hydrogel Encapsulating A20 High-Expressing Islets

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Abstract: Islet transplantation is regarded as the most promising treatment for type 1 diabetes (T1D). However, the function of grafted islet could be damaged on account of transplant rejection and/or hypoxia several years later after transplantation. We proposed a hypothetical functionalized hydrogel model, which encapsulates sufficient A20 high-expressing islets and supporting cells, and performs as a drug release system releasing immunosuppressants and growth factors, to improve the outcome of pancreatic islet transplantation. Once injected in vivo, the hydrogel can gel and offer a robust mechanical structure for the A20 high-expressing islets and supporting cells. The natural biomaterials (eg, heparin) added into the hydrogel provide adhesive sites for islets to promote islets' survival. Furthermore, the hydrogel encapsulates various supporting cells, which can facilitate the vascularization and/or prevent the immune system attacking the islet graft. Based on the previous studies that generally applied one or two combined strategies to protect the function of islet graft, we designed this hypothetical multifunctional encapsulation hydrogel model with various functions. We hypothesized that the islet graft could survive and maintain its function for a longer time in vivo compared with naked islets. This hypothetical model has a limitation in terms of clinical application. Future development work will focus on verifying the function and safety of this hypothetical islet transplantation hydrogel model in vitro and in vivo.

Keywords: islet transplantation, hydrogel, T1D, encapsulation, biomaterials

Introduction

Type 1 diabetes (T1D) is characterized by the destruction of insulin-secreting β cells by autoimmunity, which increases blood sugar (glucose) levels and results in a high incidence of life-long diabetes-related complications.^{1,2} T1D mostly affects young people and is an increasing health issue with an estimated prevalence ranged between 5% and 15% of the total cases of diabetes mellitus worldwide.³ Currently, life-long administration of exogenous insulin on daily is the primary treatment for T1D to maintain blood glucose close to the normal range and to reduce complications associated with the disease.⁴ However, insulin replacement therapy for patients with T1D cannot restore normal glucose homeostasis and leads to a high risk of secondary complications. It has been confirmed that the transplantation of pancreas or islets could reach the best therapeutic outcome.⁵ The first case of clinical pancreas transplantation was performed by Kelly et al at the University of Minnesota in the late 1960s.⁶ Since the "Edmonton protocol" with glucocorticoid-free immunosuppressive regimen was made, islet transplantation has become available for clinical treatment strategy.⁷ However, less than 20% of the transplant

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recipients remain the independence of insulin 3–5 years later after this clinical procedure.⁸ The main reason for loss of β cells after transplantation is the immune-mediated inflammatory reaction and the scarcity of oxygen. After islet transplantation, the rejection and recurrence of autoimmunity impair islet's function and eventually result in graft loss.⁹ To overcome the limitation of clinical islet transplantation, various strategies have been studied recently. It was confirmed that the hydrogel made from various biomaterials for encapsulating islets could facilitate the functionality and stability of islets.¹⁰

The hydrogel used for encapsulating islets consists of natural biomaterials and synthetic biomaterials. The natural hydrogels are biocompatible. Polymers occurring crosslinked naturally include fibrin, collagen, fibronectin, alginate, heparan sulfate, chitosan, or hyaluronic acid. Among the natural materials, alginate is widely used in islet encapsulation; it shows a degree of biocompatibility and can be crosslinked in divalent cations solution.^{11,12} Typical synthetic hydrogels include PEG (polyethylene glycol), PEG-PLA (polyethylene glycol-poly(lactic acid)), PEGDA (polyethylene glycol diacrylate) and PVA (poly(vinyl alcohol)), PHEMA-MMA (poly(hydroxyethylmethacrylate)-methyl methacrylate) and so on.¹³ In tissue engineering applications, synthetic hydrogels have advantages over natural polymer hydrogels due to their adjustable properties (eg, porosity, stability, mechanical strength, and biocompatibility).¹⁴ Among the synthetic hydrogels, PEG and its derivatives are the most widely used in islet encapsulation.^{15,16} The matrix pore size of PEG nanofilm on the surface of islet is tunable. The concentration and molecular weight of precursor PEG diacrylate can adjust the optimal pore size before gelation.¹⁷ The pore size can be adjusted to exclude large immune antibodies, while permitting glucose and insulin to pass through. Herein, PEG was introduced into the hypothetical islet encapsulating model.

Based on the size of pores in the hydrogel, the islet encapsulating models can be classified into cell penetration restrictive devices and cell-permissive devices.¹⁰ Cell penetration restrictive devices limit the migration of immune cells to pass through the pores of immune-isolating nanofilm. Through that way, the doses of immunosuppressive can be reduced or avoided when islet graft is encapsulated in cell penetration restrictive devices. Lou et al¹⁸ developed an ultrathin nanofilm of star-PEG with incorporated heparin; it protected implanted cells from host immune rejections and modified the cellular

landscape for better post-transplantation graft function and survival. Haque et al¹⁹ designed a novel method camouflaging porcine islets with PEG and its derivatives; this method could prevent islets dissociation and the invasion of various immune cells after transplantation. The camouflaged xenograft survived and sustained its function in mice for average 13.0 days. Cell-permissive devices are not equipped with the function of immune-isolating but are open to the bloodstream. Compared with cell penetration restrictive devices, the cell-permissive device can provide more oxygen and nutrition to the transplant. Different strategies for improving in situ vascularization can be applied to the cell-permissive devices, such as embedding vascular endothelial growth factor (VEGF) into the hydrogel to promote the rebuild of blood vessels.¹⁶

The hydrogel of encapsulating islet graft has emerged as an encouraging platform to eliminate the need for immunosuppressive and improve oxygen supplement, thereby allowing the wider application of islet transplant. Although encapsulated islets with various polymeric hydrogels have shown tremendous promise in many studies, some deficiencies of this technology remain unsolved.

The Deficiencies of Current Islet Encapsulation

The main obstacles of islet encapsulation are poverty of vascularization around islet graft and host immune attack activated by the transplant. The two main obstacles cause the loss of a large percentage of islets after transplantation. Islets of Langerhans are vulnerable to hypoxia. Physically, the blood supply for islets is quite abundant. Islets are around 2% of the weight of the pancreas. However, they are rendered over 5 fold higher blood flow than the exocrine pancreas.²⁰ Apart from providing nutrients and oxygen to islet, abundant blood supply enhances insulin sensitivity.²¹ The islets used for transplantation have lost its extracellular matrix (ECM) during the procedure of isolation; new blood vessels need to be established timely to maintain the survival of islets after transplanted into recipients. Cell-permissive devices are designed to maximize vascularization for islet graft encapsulated, but cannot prevent islet graft from contacting with immune cells which incurs antigen recognition by the immune system of the host.

Early islet loss after transplantation mainly results from immune rejection. The mechanism of immune rejection includes instant blood-mediated inflammatory reaction

(IBMIR).²² It is reported that 50% of islet xenografts are rejected within 9 days after transplantation without immunosuppressants in animal models.²³ Cell penetration restrictive devices can prevent infiltration and recognition of immune cells by selective permeability established by nano-sized pores on the surface of the devices. However, Brauker et al²⁴ demonstrated that 5 μm pores, compared to 20 nm pores, were 80 folds more effective in promoting the growth of vessels.

Design of the Hypothetical Hydrogel Model

We proposed a hypothetical islet transplantation hydrogel model, which serves as not only a supporting culture matrix for islets but also a drug delivery system for releasing immunosuppressants and growth factors (Figure 1). The islets encapsulated in the model are genetically modified to increase the expression of A20, which can induce immune tolerance to survive longer.

Ubiquitin editing protein A20 encoded by TNFAIP3 is a negative regulator of immunostimulatory factors.²⁵ A20 is an ideal cytoprotective gene therapy candidate for islet transplantation. Grey et al found that genetic engineering of a suboptimal islet graft with A20 preserves β cell mass and function.²⁶ Reducing expression of A20 in immune cells (eg, B cells) results in hyperactivation of the immune system.²⁷ Zammit et al²⁸ developed an islet cell line that can overexpress A20 via an adenoviral vector encoding human A20, and transplanted it beneath the kidney capsule in diabetic C57BL/6 mice. Their findings indicated that the forced expression of A20 reduced inflammation and allowed permanent islet allograft survival without the necessity of immunosuppression. A20 protects cells from apoptosis by stabilizing the linear (M1) ubiquitin network, which is associated with TNFR1 signaling complex when TNF binds to TNFR1.²⁹ Hypoxia and inflammatory cause β cell destruction in the early post-transplantation period. Genetic engineering of islets with A20 will relieve the severe poverty of islet for clinical transplantation and improve their function in the early post-transplantation period.²⁶ Benefited with the protection of A20,²⁶ a relatively reduced islet transplant mass could be available in the hypothetical model. In this model, we proposed to transfer A20 gene (TNFAIP3) into islets by a novel safer and tissue-specific recombinant adenovirus vector (rAd).²⁸ However, the toxicity of adenoviruses may impede them to be used widely.

This novel model is based on injectable hydrogel, which consists of natural biomaterials and synthetic biomaterials. As the synthetic biomaterial, PEG can provide a robust mechanical structure to the model by covalent crosslinking. Before being crosslinked, several natural biomaterials (eg, collagen, hyaluronate, and heparin) will be added into the solution of PEG to gain better biocompatibility. Once injected, hydrogel formation occurs through chemical cross-linking. Collagen, hyaluronate, and heparin are all ECM proteins, which can compensate for the loss of matrix around islets during the procedure of isolation, and mimic the physiological microenvironment of islets. Furthermore, islets can be anchored in the hydrogel through the adhesion sites on the ECM proteins, which makes the islets stable.³⁰ Among various ECM proteins, heparin is an excellent choice for the hydrogel model. Heparin can help reduce the inflammation mediated by anticoagulation, and the thiolated heparin can combine various growth factors (eg, VEGF, bFGF, PDGF, IGF-2, and KGF) by ionic bond; the growth factors can slowly release from the hydrogel model for several weeks.^{31,32}

As a drug delivery system, the model can encapsulate various growth factors. There are tremendous advantages that growth factors can bring to islets. The functionality of islets can be improved by the bond of IGF-2 and IGF-2 membrane receptors on the surface of islets. IGF-2 is a growth factor favorable for islet survival; the combination of IGF-2 and its receptor prevents islet aggregation during islet transplantation.³³ Additionally, using growth factors embedded in hydrogels can stimulate blood vessels ingrowth. Basic fibroblast growth factor (bFGF) is identified to promote angiogenesis, which is beneficial to reconstruct new capillaries around islets when transplanted into recipients. Adding bFGF into recombinant human collagen could accelerate revascularization, and reduce the hypoxia-induced damage to islets.³⁴ Various functional cells can be co-encapsulated with islets into this hypothetical model, and be co-transplanted in vivo. Mesenchymal stem cells (MSCs) are widely used to be co-transplanted with islets.^{35–39} When co-transplanted with islets in recipients, MSCs can promote angiogenesis in situ to prevent hypoxia and to attenuate immune rejection. MSCs can suppress various immune cells such as NK cells, macrophages, neutrophils, and T cells.^{35,40–43} Moreover, it was identified that MSCs could accelerate the maturation of neonatal porcine islets, which benefits the development of islets xenograft.³⁹ The establishment of immune tolerance to islet grafts, is a significant strategy for inducing

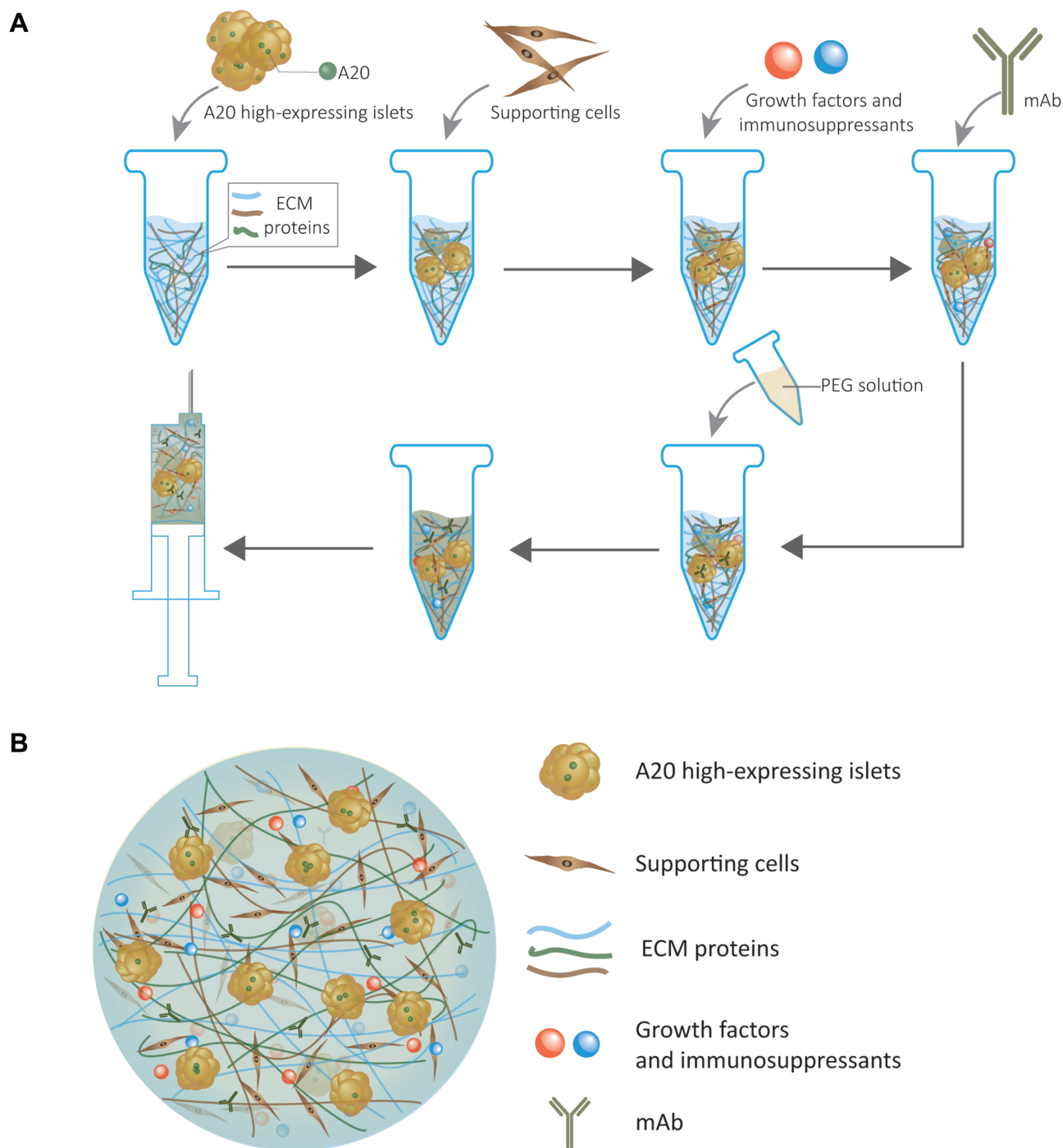


Figure 1 (A) Illustration of the hypothetical islet transplantation hydrogel model fabrication protocol. (B) Schematic illustrating the components of the hypothetical islet transplantation hydrogel model.

acceptance of histocompatibility complex (MHC)-mismatched allografts without compromising the host's immune system. T regulatory cells (Tregs) play a central role in maintaining immune homeostasis and peripheral tolerance to foreign antigens.⁴⁴ Herein, Tregs can also be added into the model as an immuno-modulatory strategy to improve islet grafts' function. Multipotent adult progenitor

cells can also be a candidate for co-transplantation with islets due to its similarities to MSCs in immunosuppressive and angiogenic advantages.⁴⁵ When transplanted with islets, endothelial progenitor cells were confirmed to promote neovascularization around the islets graft.⁴⁶

The drugs used in the immunosuppressive regimen for islets transplantation, such as sirolimus (mTOR inhibitor),

can also be encapsulated in this hydrogel. Monoclonal antibodies can also be involved. For example, the anti-CD154 blockade possesses the potency of achieving transplantation tolerance, which results in the withdraw of chemical immunosuppressants.⁴⁷ IL-2R antibody can also be added to the drug candidate list.

With the above-proposed strategies, the islet transplantation model provides a delivery vehicle for co-transplantation of A20 high-expressing islets and other supporting cells and the controlled release of immunosuppressants and growth factors. The injectable PEG hydrogel for islet encapsulation has been characterized in vitro and in vivo, illustrated the feasibility of using injectable PEG hydrogels for islet encapsulation.⁴⁸ Herein, this multifunctional hydrogel model is a covalently cross-linked injectable hydrogel. Moreover, it is flowable before gelation. Hydrogel gelation was induced by the PEG crosslinker. The PEG crosslinker must be added before injection, and gels were left for a certain time to allow for complete gelation.

Conclusion

Islet transplantation is regarded as the most promising treatment for type 1 diabetes. Unfortunately, the clinical application of islet transplantation is limited mainly due to hypoxia and the immune-mediated destruction by the host. To overcome the obstacles, we design an islet encapsulated hydrogel model with the function of the controlled release of immunosuppressants and growth factors. Sufficient A20 high-expressing islets are encapsulated in this model to reverse the condition of hyperglycemia. However, as a macro-transplantation model, it could lack oxygen in its core. Therefore, we combined several strategies to reconstruct the vascularization. Co-transplantation with supporting cells and incorporation of various growth factors are identified to be beneficial to the revascularization around transplanted islets. Also, supporting cells (MSCs) can serve as an anti-immune factor to protect islets from immune attack by host. Given to the digestion of the extracellular matrix proteins around islets during isolation, the naked islets tend to aggregate together, resulting in the increasing risk of hypoxia in the core of the islet mass and leading to the loss of islet function. To address this issue, we add various ECM proteins to the hydrogel mimicking the natural microenvironment around islets, and the islet graft will be immobilized. The hydrogel can also serve as a materials platform to immobilize growth factors. However, as a cell-permissive device, the hydrogel model permits the islet to contact blood to get sufficient oxygen, which results in IBMIR. When IBMIR

happens, the platelet will aggregate, and coagulation will occur, which are detrimental to the viability of islets.⁴⁹ The particular gene-editing islets encapsulated in the model can express a high level of A20, and the threshold for the activation of immune response will be upregulated by the activation of NF- κ B.²⁸ The application of A20 high-expressing islets can achieve long-term survival in vivo.

In summary, based on the previous studies that generally applied one or two combined strategies to protect the function of islet graft, we proposed the multifunctional encapsulation hydrogel model with various functions to achieve a better outcome of islet transplantation. This hypothetical hydrogel model was designed with cocktail therapy; the combination of various factors might promote the function of the islet graft, compensate deficiency for each other. This hypothetical model might be injected into several suitable sites in vivo, such as the beneath of kidney capsule, the peritoneal cavity, and a subcutaneous site on the back.^{48,50} In the model, the hydrogel will be injected into body before gelation, then capillaries will creep into the hydrogel. With the release of immunosuppressants embedded in the model, the local immune isolation will be established. This hypothetical multifunctional hydrogel model has a limitation in terms of clinical application. Future development work will focus on verifying the function and safety of this hypothetical islet transplantation hydrogel model in vitro and in vivo.

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Disclosure

The authors declare no potential conflicts of interest for this work.

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