Accepted Manuscript

Design of a vascularized synthetic poly(ethylene glycol) macroencapsulation device for islet transplantation

Jessica D. Weaver, Devon M. Headen, Michael D. Hunckler, Maria M. Coronel, Cherie L. Stabler, Andrés J. García

PII: S0142-9612(18)30311-9

DOI: 10.1016/j.biomaterials.2018.04.047

Reference: JBMT 18633

To appear in: *Biomaterials*

Received Date: 12 February 2018

Revised Date: 19 April 2018

Accepted Date: 23 April 2018

Please cite this article as: Weaver JD, Headen DM, Hunckler MD, Coronel MM, Stabler CL, García AndréJ, Design of a vascularized synthetic poly(ethylene glycol) macroencapsulation device for islet transplantation, *Biomaterials* (2018), doi: 10.1016/j.biomaterials.2018.04.047.

Design of a vascularized synthetic poly(ethylene glycol) macroencapsulation device for islet transplantation

Jessica D. Weaver[a], Devon M. Headen[a], Michael D. Hunckler[a], Maria M. Coronel[a], Cherie L. Stabler[b], Andrés J. García[a†]

a. Woodruff School of Mechanical Engineering and Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, GA 30332, USA
b. Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611, USA
† Corresponding author. Email address: andres.garcia@me.gatech.edu

Keywords: islet transplantation, vascularization, encapsulation, omentum transplantation

Abstract

The use of immunoisolating macrodevices in islet transplantation confers the benefit of safety and translatability by containing transplanted cells within a single retrievable device. To date, there has been limited development and characterization of synthetic poly(ethylene glycol) (PEG)-based hydrogel macrodevices for islet encapsulation and transplantation. Herein, we describe a two-component synthetic PEG hydrogel macrodevice system, designed for islet delivery to an extrahepatic islet transplant site, consisting of a hydrogel core cross-linked with a non-degradable PEG dithiol and a vasculogenic outer layer cross-linked with a proteolytically sensitive peptide to promote degradation and enhance localized vascularization. Synthetic PEG macrodevices exhibited equivalent passive molecular transport to traditional microencapsulation materials (e.g., alginate) and long-term stability in the presence of proteases *in vitro* and *in vivo,* out to 14 weeks in rats. Encapsulated islets demonstrated high viability within the device *in vitro* and the incorporation of RGD adhesive peptides within the islet encapsulating PEG hydrogel improved insulin responsiveness to a glucose challenge. *In vivo*, the implementation of a vasculogenic, degradable hydrogel layer at the outer interface of the macrodevice enhanced vascular density within the rat omentum transplant site, resulting in improved encapsulated islet viability in a syngeneic diabetic rat model. These results highlight the benefits of the facile PEG platform to provide controlled presentation of islet-supportive ligands, as well as degradable interfaces for the promotion of engraftment and overall graft efficacy.

1. Introduction

Type 1 diabetes (T1D) mellitus, characterized by the autoimmune destruction of insulin-secreting beta cells within pancreatic islets, affects 1.25 million individuals in the United States [1], resulting in a $15 billion annual financial burden [2]. Current treatment for T1D is limited to exogenous insulin injections, which cannot adequately restore normal glycemic control, resulting in a high incidence of long term secondary complications [3]. Islet cell replacement therapy has demonstrated the ability to restore native insulin signaling patterns and has the potential to eliminate long term complications of the disease [4, 5]. The required chronic systemic immunosuppression regimen for this allogeneic organ transplant, however, is an unrealistic burden for the vast majority of T1D patients [6], necessitating alternative strategies to mitigate immune rejection of transplanted islets that can widen the applicability of this transformative therapy for insulin-dependent patient populations [7].

Encapsulation of transplanted cells within biomaterials has long been proposed as a method of circumventing chronic systemic immunosuppression by preventing the cell-to-cell contact that results in direct antigen recognition by the immune system [8-10]. This strategy spans the scale of nano-, micro-, and macro-encapsulation [11, 12]. Microencapsulation is the most heavily investigated strategy, wherein 1-3 islets are commonly encapsulated within a hydrogel and delivered to the intraperitoneal space [9], due to the space required by the volume of such a graft [13]. To date, there has been limited translational success of microencapsulation due to lack of graft function, as well as safety limitations of non-retrievable capsules within the intraperitoneal space. Human trials demonstrate microcapsule adhesion to parietal peritoneum, spleen, kidney, and omentum, raising concerns about the long-term safety of intraperitoneal capsule delivery [14].