Vasculogenic Degradable Hydrogel to Enhance Islet Engraftment, Function, and Survival within Extrahepatic Transplant Sites

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Introduction

Type 1 diabetes affects millions worldwide, and while exogenous insulin improves life expectancies, patients face high rates of secondary complications[1]. Islet transplantation is a promising alternative therapy that can potentially restore native insulin signaling and eliminate secondary complications of diabetes, but widespread application is hindered in part by a non-ideal intrahepatic islet transplant site that contributes to massive early graft loss and instability[2]. Various alternative sites for donor islets have been explored, including the subcutaneous (SUBQ), small bowel mesentery (SBM) and omentum, or equivalent murine epididymal fat pad (EFP), sites. Key characteristics of an ideal alternative transplant site include low mechanical forces, graft retrievability, and a high degree of vascularization[3]. Recapitulation of the islet organoid's native vascular network in the host is pivotal to transplanted islet engraftment[4], with vasculogenic endothelial growth factor (VEGF) demonstrating a crucial role in islet revascularization[5]. To that end, we developed a VEGF-bound proteolytically degradable polyethylene glycol (PEG) hydrogel system for islet delivery to diverse extrahepatic transplant sites, and we demonstrate that localized vascular bed enhancement correlates with improved islet engraftment, survival, and glycemic control.

Methods

Single pancreatic donor islet mass (600 IEQ) were delivered to the SUBQ, SBM, or EFP sites in gels (4-arm PEG-Maleimide (20kDa) gels (50 µL) modified with RGD adhesive peptide and VEGF) in diabetic recipient mice.

Results & Discussion

Vasculogenic PEG-based hydrogels enhanced vascularization within extrahepatic sites, and improved glycemic control of a single pancreatic donor islet mass in syngeneic transplants. To confirm that vasculogenic gels enhanced islet survival within extrahepatic sites, resulting in improved glycemic control, islets constitutively expressing luciferase were delivered and tracked over a five week period (Fig. 1a). Quantification of overall islet signal (Fig. 1b) demonstrates vasculogenic gels enhance islet survival in both EFP and SUBQ sites over control PEG gels. Of note, an intrahepatic control reflecting the current clinical islet delivery method, demonstrates the drastic improvement of islet survival in extrahepatic sites over the current clinical technique.

Conclusion

We demonstrate herein a relationship between degree of vascularization and islet engraftment and survival within an extrahepatic transplant site, as well as a facile method for delivering vasculogenic factors to the transplant site via an in situ, synthetic hydrogel islet delivery system.

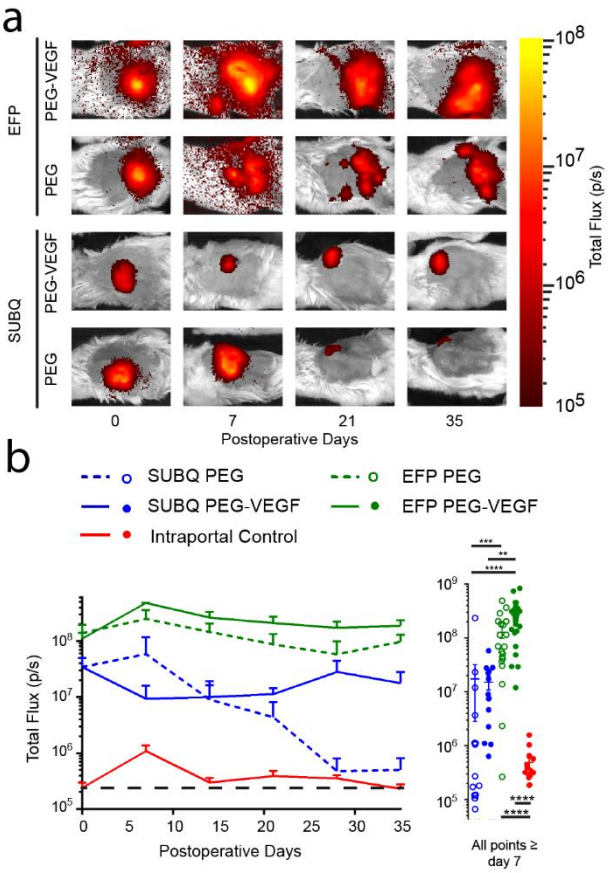

Figure 1 Vasculogenic hydrogels enhance islet survival in extrahepatic transplant site, as demonstrated by real-time in vivo bioluminescent tracking (a), and quantification of bioluminescent islet signal (b). **** P < 0.0001, *** P < 0.001.

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