A bio-inspired hybrid nanosack for the delivery of pancreatic islets and FGF-2 to improve islet engraftment at the omentum site

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Statement of Purpose

A major limitation for the practical implementation of pancreatic islet transplantation (PIT) as a cure for diabetes is substantial islet cell death during the peritransplant period and therefore limited engraftment after the transplant. In this regard, the interactions between islet cells and the extracellular matrix (ECM) are critical for β-cell viability and function. In addition, significant islet destruction occurs following exposure to blood during islet embolization into the portal vein (the only accepted site for PIT). Thus, alternative extrahepatic sites are necessary. The omentum site is an attractive extrahepatic site for PIT as it allows a large implantation volume, the concurrent use of transplant devices, and some immune privilege. However, revascularization is one of the major challenges at the omentum site due to its low vascularity. Therefore, new strategies to provide an islet ECM mimicking microenvironment to enhance islet survival, function, and engraftment as well as to stimulate islet revascularization at the omentum site are needed. In order to develop the new strategy of PIT, first, we propose to test an ECM mimic self-assembled nanomatrix gel which can encapsulate islets and provide a protective and nurturing environment through a cell adhesive ligand for islet survival and enzyme-mediated degradation for engraftment. Secondly, to enhance islet revascularization at the omentum site, a hybrid nanosack was fabricated to deliver islets and FGF-2, and implanted in the rat omentum to evaluate angiogenesis surrounding the hybrid nanosack in the omentum.

Research Design and Methods

To evaluate a peptide amphiphile (PA) nanomatrix gel enhancing islet survival and function, three culture groups were designed: 1) bare group: isolated rat islets cultured in 12 well non-tissue culture treated plates, 2) insert group: isolated rat islets cultured in modified insert chambers, and 3) nanomatrix group: isolated rat islets encapsulated within the PA nanomatrix gel and cultured in modified insert chambers. Over 14 days, insulin response to glucose stimulation was measured, and islet viability and function were assessed by fluorescein/propidium iodide (FDA/PI) and dithizone staining. Next, to create the hybrid nanosack, FGF-2 was encapsulated within the PA nanomatrix gel and wrapped within the e-PCL nanofiber sheet with crater like structures coated with FGF-2. The hybrid nanosack was implanted to the rat omentum. After 2 weeks of implantation, μ-CT analysis was performed to visualize anigiogenesis at the omentum area.

Results

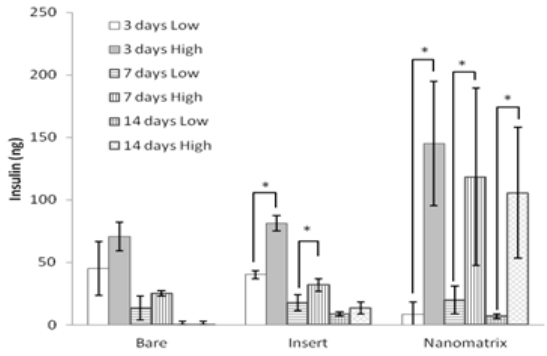

Fig. 1. Glucose-stimulated insulin secretion for 14 days of cultivations (*: significant differences between low glucose (3mM) and high glucose (20mM) incubation, $p<0.05$) (n=4).

As shown in *Fig. 1*, although there was a marked decrease in insulin secretion for the bare and insert groups, glucose-stimulated insulin secretion was maintained in the nanomatrix group, even after 14 days. Also, these results were verified by FDA/PI to assess viability and dithizone to observe insulin functions.

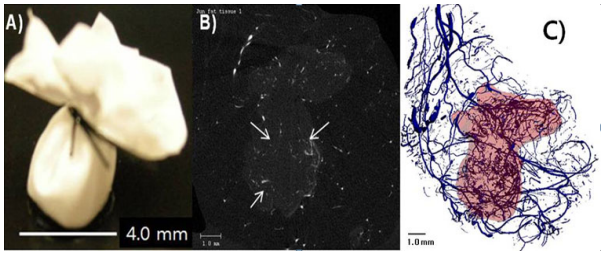

Fig. 2. a) Hybrid nanosack b) acquired sectioned 2D and c) 3D μ-CT images of implanted hybrid nanosack in the omentum of a rat after 2 weeks.

Fig. 2 shows that angiogenesis occurred surrounding the hybrid nanosack in the omentum. Arrows in b) indicate micro-blood vessels invaded the hybrid nanosack and purple vessels in c) also demonstrate that high density vasculatures were generated within the hybrid nanosack.

Conclusion

The self-assembled PA nanomatrix gel maintained prolonged islet function and viability for up to 14 days. In addition, we have successfully developed the hybrid nanosack which enhanced revascularization at the omentum site of rat. Therefore, these novel strategies have great potential to promote islet survival, engraftment, and stable long term function at the omentum site.

References: 1. Lim. D. J of Tissue Eng. 2011. 17 (3-4): 399-406. 2. Lim. D. J of Micro Nano Letters. 2011. 6 (8): 619-623.

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