

Enhanced rat islet function and viability within a biomimetic self-assembled nanomatrix gel

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Statement of Purpose

Pancreatic islet transplantation (PIT) has been given increasing attention as an alternative treatment for insulin-dependent diabetes mellitus, but a few limitations to its success in clinical trials have been identified. In particular, the substantial loss of islets is reported as one of primary causes of islet graft failure because the destruction of extracellular matrix (ECM) around islets causes reduced beta-cell function and survival.¹ To enhance the efficacy of PIT, there is an imperative need to develop an ECM mimicking material capable of providing the islet with a protecting and nurturing microenvironment. Therefore, we have developed a self-assembled peptide amphiphile (PA) nanomatrix gel that is inscribed with cell adhesive ligands as well as enzyme-mediated degradable sites to restore islet-ECM interactions. To confirm the potential of the nanomatrix gel for PIT, function and viability of rat islets were evaluated *in vitro*. Renal subcapsular islet transplantation was also performed using a streptozotocin (STZ)-induced diabetic rat model.

Methods

Hand-picked rat islets were cultured over 14 day cultivation period within/without the self-assembled PA nanomatrix gels. Glucose stimulated insulin secretion was measured for 14 days. Islet viability was assessed with a fluorescein diacetate/propidium iodide (FDA/PI) staining, and insulin production in islets was assessed with a dithizone (DTZ) staining. To evaluate the efficacy of nanomatrix gels for PIT, 1500 syngeneic rat islets were encapsulated within the nanomatrix gel and transplanted into the left renal subcapsule of STZ-induced diabetic rats. Non-fasting blood glucose levels were recorded for 22 days after transplantation and intraperitoneal glucose tolerance test was performed at 22 days after transplantation.

Results

PA consisting of a cell adhesive ligand RGDS, an enzyme-mediated degradable site specific for metalloproteinase-2, and a hydrophobic alkyl tail were synthesized using standard Fmoc-chemistry on an Advanced Chemtech Apex 396 peptide synthesizer as described previously.² Isolated rat islets were cultured for 14 days within/without the nanomatrix gel. For bare islets without the nanomatrix gel, there was a marked decrease in glucose-stimulated insulin secretion, whereas islets encapsulated within the nanomatrix gel showed relatively maintained function, even after 14 days (Figure 1). There was no positive DTZ staining in the bare group after 14 days, whereas islets within the nanomatrix group still maintained high positive staining. FDA/PI staining results also showed that the islets in the nanomatrix gel group still maintained islet integrity and that all remained viable. Hence, these results indicate that the nanomatrix gel group maintained function throughout the 14 days.

Based on the *in vitro* results, 1500 rat islets with/without the nanomatrix gel were transplanted into the renal subcapsule of the STZ-induced diabetic rats. The recipient rat with islets within the nanomatrix gel showed a significant low level of blood glucose, even 1 day after transplantation. Rats receiving islets without the nanomatrix gel maintained high glucose levels, whereas there was the trend of significant reduction in blood glucose levels within the nanomatrix gel group. Moreover, there are significant differences in intraperitoneal glucose tolerance tests (IPGTTs) at 22 days after transplantation between the islets embedded within the nanomatrix gel group and the islets without the nanomatrix gel group. These results indicate that the nanomatrix gel would improve the renal subcapsular islet graft.

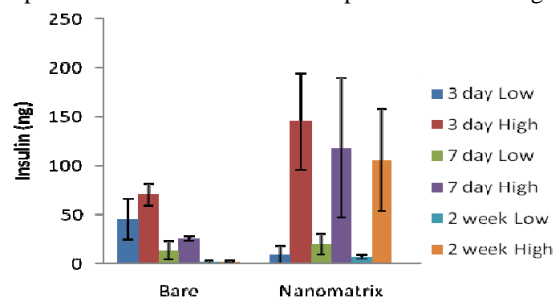


Fig. 1. Glucose-stimulated insulin secretion for 14 days of cultivations ($p < 0.05$) ($n = 4$).

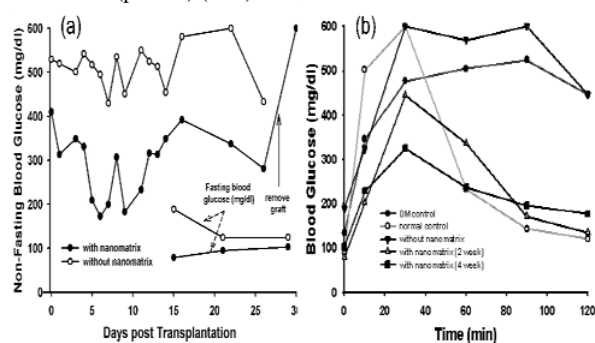


Fig. 2. a) Non-fasting blood glucose levels for 22 days after transplantation. b) Intraperitoneal glucose tolerance test at 22 days after transplantation.

Conclusion

After a 14 day culture period, rat islets embedded in the PA nanomatrix gel showed significantly enhanced viability and glucose-stimulated insulin secretion response compared to control. Also, *in-vivo* results demonstrated that the nanomatrix gel has a great potential to improve the engraftment of syngeneic islets in the kidney capsule by creating a nurturing and protective microenvironment for islets.

References

1. Wang, R N, Rosenberg, L. J Endocrinol 1999 181-90.
2. Anderson, JM et al. ACS Nano 2009 3447-54.