Mesenchymal Stem Cells and Ligand Incorporation Modulate Pancreatic Islet Function and Apoptosis in PEG Hydrogel Scaffolds

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Statement of Purpose: Type 1 diabetes (T1D) is an autoimmune disease resulting in elevated levels of glucose in blood circulation due to lack of insulin secretion function of beta cells in the pancreas [1]. To date, various strategies have been employed for micro- or macro- encapsulation of pancreatic islets to prevent from immune attack and further, ligand incorporation have been used as a common strategy to improve function and survival of pancreatic islets in both synthetic and natural networks. These studies have shown that PEG hydrogels are ideal candidates for the treatment of T1D [2, 3], however influence of an antiapoptotic companion cell on islets within biofunctionalized PEG hydrogel network has not been investigated. Here, we studied the role of extracellular matrix derived peptides (RGDS and IKVAV), GLP-1 and bone marrow derived mesenchymal stem cells in islet encapsulated within PEG hydrogel scaffolds to distinguish the influence of peptides and stem cells on islet function and apoptosis.

Methods: A water-based prepolymer solution including poly(ethylene glycol) diacrylate (PEGDA), triethanolamine (TEA), N-vinylpyrrolidone (NVP), eosin Y and acrylated peptides (RGDS, IKVAV and GLP-1) were used to produce unmodified and modified PEG hydrogels (Fig. 1). Before the synthesis of scaffold under visible light (514 nm), islets and stem cells were suspended in PEG hydrogel prepolymer solution.

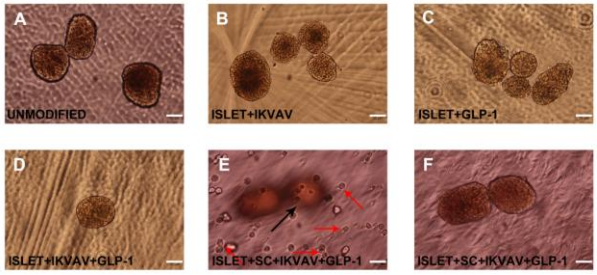

Figure 1. Encapsulation of islets and mesenchymal stem cells within PEG hydrogels. Black and red arrows point islets and rBM-MSCs, respectively. Scale bars= 50 µm.

Alterations in ATP concentration (Cell-Titer Glo), caspase activity (Caspase Glo) and insulin secretion (static incubation and ELISA) on day 3 were examined as indicators of the effects of each condition.

Results: The results in this study showed that the presence of covalently incorporated ligands in PEG hydrogels significantly decreased islet apoptosis. As demonstrated in Fig. 2, ATP concentration was higher, while lower caspase activity was measured in ligand functionalized PEG hydrogels. Significant influence was observed in the presence of all three peptides (RGDS, IKVAV and GLP-1). This could be occurring as a result of diverse interactions of each individual peptide with islet cells, and hence generated a synergistic effect.

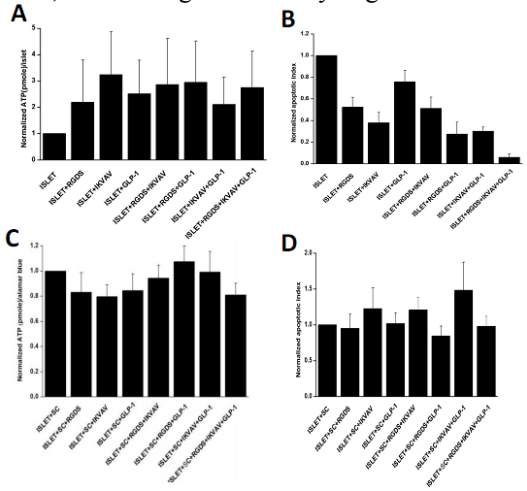

Figure 2. Antiapoptotic role of adhesion peptides, GLP-1 (A & B) and stem cells (C & D) on islets in PEG hydrogels.

In the case of coencapsulation with mesenchymal stem cells, no significant differences in ATP concentration and caspase activity were observed compared to unmodified PEG hydrogels (Fig. 2). Incorporation of both stem cells and ligands, into the network resulted in major improvements in insulin secretion function of islets (Fig. 3), which will be very important for long term survival and function for encapsulated islets that could be implanted for the treatment of diabetes.

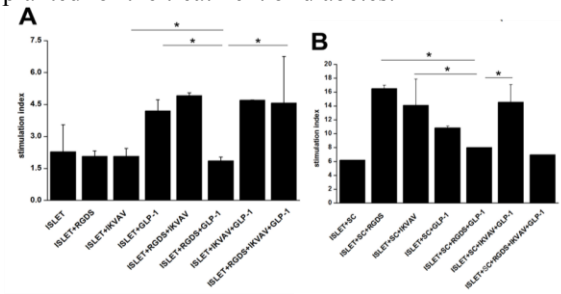

Figure 3. Role of mesenchymal stem cells and peptides in islet function in PEG hydrogel networks.

Conclusions: The results in this study indicate that the presence of the antiapoptotic stem cells could be used as a promising tool to improve the survival and function of pancreatic islets and hence can reduce the number of islets required for clinical transplantation.

References:

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