Scaffolds Engineered to Release TGF-β1 Improve Islet Graft Function

R. Michael Gower[1], Jesse Zhang[1], Jeffrey Liu[1], Lonnie D. Shea[1]
[1]Northwestern University Chicago, IL

Statement of Purpose: A central component for many tissue-engineering approaches is a biomaterial scaffold, which provides a tool to modulate the local environment with the objective of promoting development of endogenous or transplanted cells into functional tissues. Scaffolds that provide a platform for islet transplant have been developed and reverse diabetes with a fraction of the islets isolated from a mouse pancreas. However, immune rejection of transplanted islets must be prevented by immunosuppressive drugs, which increase susceptibility to infection and cancer. An alternative strategy to systemic immunosuppression is to modulate the immune environment within the transplant site to promote tolerance to the graft. In pursuit of this goal, scaffolds were developed that release recombinant TGF-β1, a protein with immunoregulatory functions. Studies were carried out to investigate the effect of TGF-β1 delivery on the frequency and activation state of immune cells within the scaffold and the efficacy of this strategy to extend islet function in an allogeneic transplant model.

Methods: TGF-β1 loaded poly(lactide-co-glycolide) (PLG) scaffolds were comprised of three layers, two porous outer layers and a non-porous center layer containing protein. The non-porous center layer was made by combining PLG microspheres with recombinant TGF-β1 and lyophilizing the mixture. The outer layers were made by mixing PLG microspheres with salt particles. The three layers were pressed together in a steel die using a Carver press and gas-foamed after equilibration in high pressure CO_2. Salt particles were then removed by washing in water. Islets were isolated from healthy BALB/c mice, seeded onto scaffolds, and implanted into the peritoneal fat of C57BL/6 mice rendered diabetic by streptozotocin injection. Graft function was monitored by blood glucose measurements. Flow cytometry was used to phenotype immune cells within the scaffold.

Results: Flow cytometry of cells isolated from TGF-β1 scaffolds implanted into the peritoneal fat indicated that the number of immune cells was decreased by over 60% compared to scaffolds with no protein, demonstrating that TGF-β1 was a potent suppressor of immune cell infiltration into PLG scaffolds following implant. Islets transplanted on TGF-β1 scaffolds restored normoglycemia and maintained normal blood glucose levels for a significantly longer period of time compared to islets transplanted on blank scaffolds (19 versus 12 days). Flow cytometry of islet grafts indicated that TGF-β1 delivery resulted in a significant decrease in the number of macrophages (67% decrease), natural killer cells (45% decrease), and dendritic cells (45% decrease) within the graft. Conversely, CD4 and CD8 T cell numbers were not significantly impacted by TGF-β1 delivery. Taken together these results suggest that extended islet function on TGF-β1 scaffolds was due to inhibition of innate immune cell mediated destruction of the allografts.

Conclusions: Islets transplanted on TGF-β1 releasing scaffolds are able to restore normoglycemia and function significantly longer than islets transplanted on blank scaffolds because of delayed immune rejection. As cell-based therapies become prevalent, due in part to advances in stem cell technology, modulation of the immune response will be necessary to prevent rejection. Approaches for controlling the local immune environment, such as directing activation and migration of immune cells, may be a promising alternative to systemic immunosuppression for regenerative medicine.