Biosynthetic Materials for Islet Encapsulation and Transplantation

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Hydrogels, highly hydrated cross-linked polymer networks, have emerged as powerful synthetic analogs of extracellular matrices for basic cell studies as well as promising biomaterials for regenerative medicine applications. A critical advantage of these synthetic matrices over natural networks is that the biophysical and biochemical properties of the material can be tuned with high control and precision. For example, bioactive functionalities, such as cell adhesive sequences and growth factors, can be incorporated in precise densities. We have engineered poly(ethylene glycol) [PEG]-maleimide hydrogels that support improved pancreatic islet engraftment, vascularization and function in diabetic models. Two biomaterial strategies will be discussed. We have developed proteolytically degradable synthetic hydrogels, functionalized with vasculogenic factors for localized delivery, engineered to deliver islet grafts to extrahepatic transplant sites via in situ gelation. These hydrogels induce differences in vascularization and innate immune responses among subcutaneous, small bowel mesentery, and epididymal fat pad transplant sites with improved vascularization and reduced inflammation at the epididymal fat pad site. This biomaterial-based strategy improves the survival, engraftment, and function of a single pancreatic donor islet mass graft compared to the current clinical intraportal delivery technique. In a second application, we have developed a localized immunomodulation strategy using hydrogels presenting an apoptotic form of Fas ligand (SA-FasL) that results in prolonged survival of allogeneic islet grafts in diabetic mice. A short course of rapamycin treatment boosts the immunomodulatory efficacy of SA-FasL-hydrogels, resulting in acceptance and function of allografts over 200 days. Survivors generate normal systemic responses to donor antigens, implying immune privilege of the graft, and have increased T-regulatory cells in the graft. This localized immunomodulatory biomaterial-enabled approach may provide an alternative to chronic immunosuppression for clinical islet transplantation.