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Islet and cell surface modification as a novel immunotherapy for islet transplantation

Genetic manipulation of donor pancreatic islet grafts ex vivo to express immunomodulatory molecules as a means of preventing rejection and/or inducing transplantation tolerance represents an exciting approach that may obviate the use of chronic immunosuppression and associated toxicity in graft recipients. However, introduction of recombinant genetic material into islets faces various challenges that need to be overcome for the routine application of gene therapy in clinical islet transplantation. This raises the question whether selected goals of gene therapy can be achieved by the transient display of exogenous proteins with immunomodulatory functions on islet cells. We, therefore, developed a novel method designated ProtEx™ to achieve this goal. In designing this method, we made use of the high affinity interaction ($K_d=10^{-15}$ M) of streptavidin with biotin. Once formed, this noncovalent complex dissociates very slowly and in theory can be exploited to achieve long-term display of proteins chimeric with streptavidin/avidin on the surface of any cell, tissue or organ of interest that have been modified with biotin. This method involves the generation of chimeric proteins with core streptavidin, cell surface modification with biotin, and decoration of biotinylated cells, tissues or organs with chimeric proteins (**Fig. 1**). In testing this concept, we generated a novel form of the FasL molecule chimeric with streptavidin (SA-FasL) with potent apoptotic activity on Fas^+ lymphocytes. In previous studies, we demonstrated that systemic immunomodulation with donor splenocytes engineered to display FasL on their surface resulted inhibition of primary and memory alloreactive immune responses and tolerance to cardiac allografts (Yolcu *et al. J. Immunol.* 181:931-9, 2008). In the present study, we tested whether pancreatic islets can be engineered to display on their surface FasL and if FasL-engineered islets have any survival advantage following transplantation into chemically diabetic hosts. We report that pancreatic islets can be engineered ex vivo in a rapid and effective manner to display the FasL protein on their surface. FasL-engineered islets established euglycemia following transplantation into chemically diabetic syngeneic host without detectable toxicity. Importantly, FasL-engineered islets when transplanted into chemically diabetic allogeneic hosts under the transient cover of rapamycin established and maintained euglycemia in hundred percent of graft recipients over 500 days observation period. Mechanisms responsible for long-term islet graft survival will be discussed during this presentation. Engineering pancreatic islets to display on their surface the SA-FasL protein in a rapid and effective manner represents a practical and safe alternative to gene therapy for immunomodulation to induce transplantation tolerance.

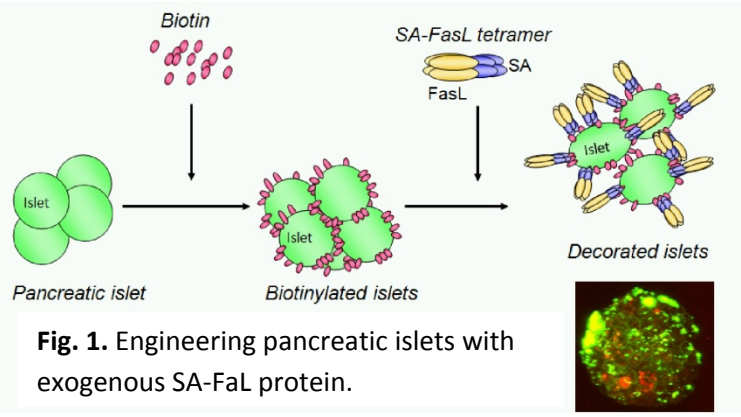

Fig. 1. Engineering pancreatic islets with exogenous SA-FaL protein.