Stealth Cell Delivery for Self-Regulating Glucose Level

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Pancreatic islet cell therapy is an attractive method for treating type 1 diabetes mellitus. However, the transplanted islets are easily susceptible not only to allogeneic recognition and rejection but also to recurrence of autoimmunity. They are also damaged by nonspecific inflammatory events that occur in the microenvironment at transplantation site. Recently, we have developed a new immunological protective strategy to protect transplanted islets from immune reaction, which is poly(ethylene glycol) (PEG) conjugation onto the islet surface. Our hypothesis is that the conjugated PEG could directly repel the immune cells or cytotoxic cytokines due to the hydrophilicity of PEG. When the PEGylated islets were cultured *in vitro* with immune cells such as lymphocytes, macrophages or splenocytes, the viability or functional activity of them was not damaged. Also, when the PEGylated islets were transplanted under the subcapsular membrane of kidney, they were well preserved. In addition, the synergistic effect of PEGylation to islet surface was evaluated by administration of an immunosuppressant cyclosporine A, one of widely used immunosuppressive drugs, after PEGylated islets transplantation in the diabetic rats. During daily treatment of 3 mg/kg of CsA, unmodified islets (control) were completely rejected within two weeks, while PEGylated islets are still on surviving and functioning for one year to normally control the blood glucose level of animals. Also, the long-term survived PEGylated islets could have normal blood glucose responsiveness and insulin synthesis. On the other hand, when heme oxygenase-1 (HO-1), one of the cytoprotective defense responses against oxidative injury, was systemically overexpressed by injection of cobalt chloride after islets transplantation, the unmodified islets were also completely rejected within two weeks. However, the survival time of PEGylated islets significantly increased. In conclusion, our findings demonstrated that the PEGylation onto islet surface could reduce the immunogenecity of islets and protect the islets from host's immune reactions. In addition, immunological protective effect of PEGylation could have synergism for a long time period when combined with low dose of CsA and/or HO-1 overexpression. Therefore, this PEGylation onto islet surface is a novel immunological protective approach in clinical application as stealth cell delivery.