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Local immunomodulation by Jagged-1 for islet graft acceptance

Type 1 diabetes is a chronic autoimmune disease with a high economic burden worldwide ($327 billion in 2017). Although transplantation of pancreatic islets is a promising approach for treatment of type 1 diabetes mellitus, the engraftment efficiency of these islets is limited by host immune responses. Regulation of these immune responses at the graft site is pivotal to prevent an excessive immune response. Immunoisolation of islets is an attractive approach to restrict application of systemic immunosuppressive therapy and prevent its side effects. Nevertheless, the antigens shed by islets form a physical barrier and cytokines in the local microenvironment can induce the immunological response cascade. Induction of regulatory cells as anti-inflammatory cells around the graft has been introduced to regulate immune cell responses for graft acceptance. Local delivery of these factors at the graft site is an efficient method for regulation of these response and it might be a promising alternative route to achieve the successes in islet transplantation.

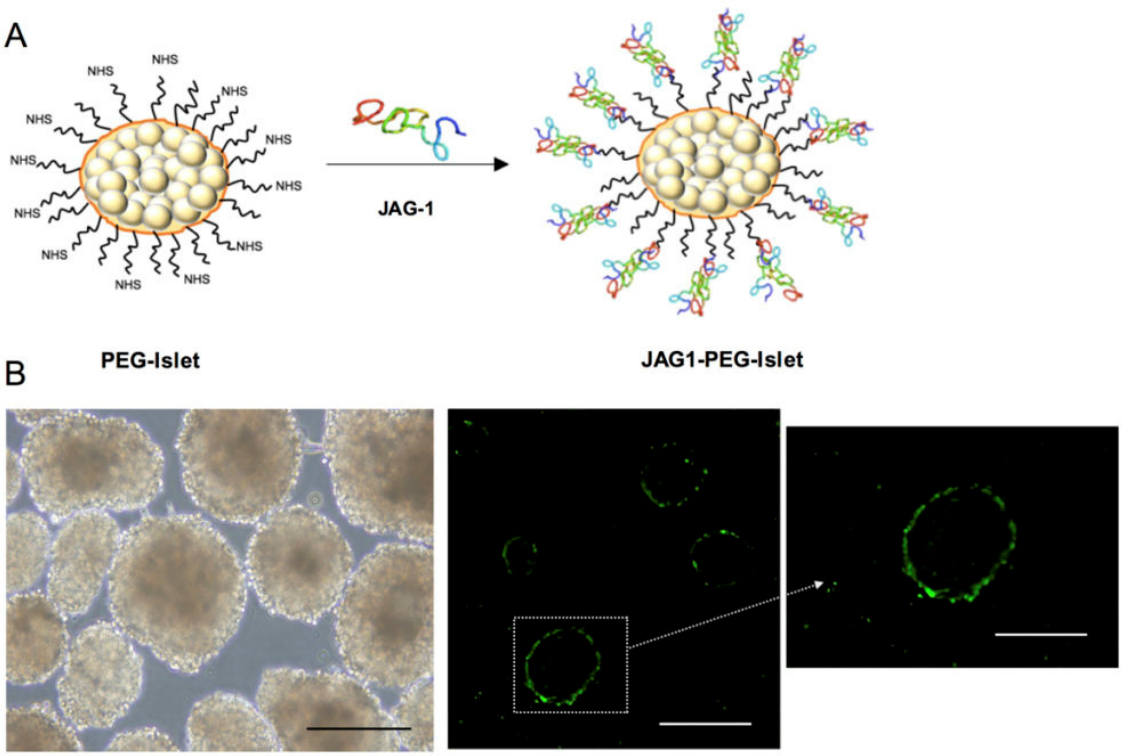

Fig. 1. Immobilization of jagged-1 (JAG-1) onto PEGylated islets. (A) Schematic illustration of JAG-1 conjugation after PEGylation of the islets (B) Light microscopic images of PEGylated islets (Left) and confocal microscopy images of JAG-1 conjugated on PEGylated islet surface (Right). Scale bar: 200 μM.

Tumor cells are an interesting model because of the methods that they use to escape from immune system responses. By understanding how tumors evade immune surveillance, we got an idea to design a strategy that provide immunoprotection for the graft. One of the main mechanisms of tumor evasion is JAG-1 ligand overexpression. According to different studies, JAG-1 plays a potential role in induction of regulatory cells

and consequently modulates the tumor microenvironment by generation of anti-inflammatory agents and the survival of tumor.

Thus, we have developed a surface engineering approach for the islet microenvironment. Jagged-1 (JAG-1) was immobilized on the islet surface by mediation of a double-layer of poly(ethylene glycol) (PEG) polymer. Immobilization and functionality of JAG-1 on PEGylated islet surfaces were established.

When co-cultured with splenocytes, the JAG-1 conjugated islets induced a significant increase in regulatory cells and regulated the cytokine levels produced by immune cells. The results demonstrated that JAG-1 immobilization could improve immunoprotection of pancreatic islets by localized modulation of the immune milieu from an inflammatory to an anti-inflammatory state. We also evaluated the effects of surface modification of these islets by JAG-1 in a xenotransplantation model. The transplanted JAG-1-modified islet group showed a significantly reduced blood glucose levels compared with the control group of diabetic mice during the acute phase of the immune response to the transplanted islets. Overall, our study has demonstrated that immobilization of JAG-1 onto the PEGylated islet surface promoted a anti-inflammatory microenvironment.

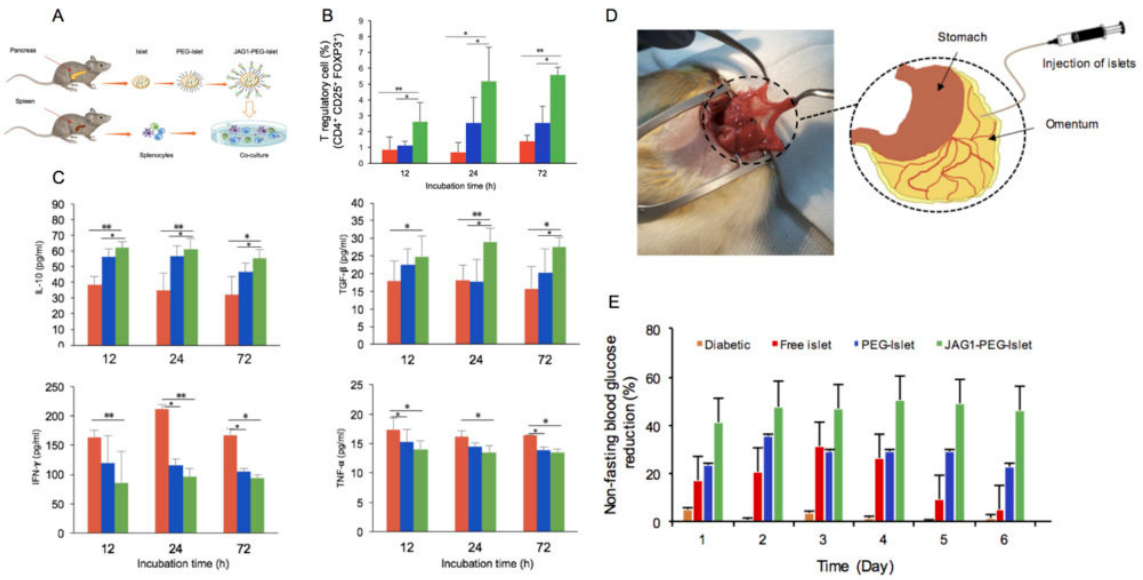

Fig. 2. Induction of an immunomodulatory microenvironment in the presence of jagged-1 (JAG-1) conjugated on the PEGylated islets and islet transplantation in diabetic mice model. (A) Schematic of surface modification of islets and co-culture with splenocytes. (B) Assessment of CD4+CD25+FOXP3+ cells (Tregs) after co-culture of splenocytes with the islets. (C) Measurement of cytokine levels for 12, 24, and 72 h incubation periods. (D) Islet transplantation into the omentum of a diabetic mice model (E) Percentage of non-fasting blood glucose that reduced in mice treated with islets during the 6 days post-transplantation.

In summary, the present study offers a new procedure for surface engineering of islet cells and it is a proof of concept to determinate the effect of conjugated JAG-1 ligands onto the pancreatic islet surface and their

acceptance. This approach opens new opportunities for localized immunoprotection of pancreatic islets and other allogeneic cell therapies in the future.

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Publication

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