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Chimeric pseudoislets development method that retains beta cell features

Mature pancreatic islets are the gold standard for transplantation-based approaches for islet replacement in type 1 and type 3c diabetes mellitus (T1D and T3cD), but this feature is offset by the scarcity of human cadaveric pancreas donors. Thus, global efforts are directed to develop replacement islets from renewable sources like human stem cell lines. Despite progress in this area, stem cell-derived replacement islets (SCRIs) lack functional maturation, and recent work has identified molecular, signaling and genetic features of this incomplete development. This includes evidence for GPCR-based signaling between islet cells during fetal development, and expression of crucial factors like the transcriptional regulators in normal human islet beta cell maturation. Islet development in humans and other vertebrates involves aggregation of individual islet cells into multicellular islets to produce heterogeneous clusters of beta, alpha, and delta cells, and other non-islet cell types. Thus, from their birth, interactions between islet cells likely guide islet development. However, the mechanisms of intra-islet signaling to foster human islet development and maturation remain poorly characterized.

To address this knowledge gap, inventors at Stanford have exploited the use of pseudoislets to mix SCRI cells and native human islet cells to create mixed chimeras. By using molecular and electrophysiological assays, they showed that exposure of SCRI beta cells to native islet cells in such in vitro cell mixtures substantially enhances their molecular and functional maturation. The invention disperses cells from stem-cell-derived protocols, and mixes these with dispersed bona fide islet cells from adult donors (human or pig). They are then cultured briefly before being re-isolated into the stem cell-derived progeny resembling islet beta-cells. When re-isolated, these show improved features including production of maturity markers and improved function. These pseudoislets have been demonstrated to function and be transplantable in diabetic animals. The invention

identifies a process to provide crucial signals for islet maturation and can be applied for development of replacement islet beta cells or other islet cell types.

Applications

- Stem cell-derived replacement islets for diabetes
- Renewable human beta cells

Advantages

- Retains key features of native human beta cells, including SIX2 and SIX3 production that stimulate beta function and specialization
- Improved features including production of maturity markers and improved function
- Biocompatible and transplantable in vivo

Patents

- Published Application: WO2024118731

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