Double Gene Knockout of PDX-1 and HNF1β Leads to Possible Novel Gene Therapy for Type 1 Diabetes

Kathryn Kosiorek
Longwood University
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Department of Biological and Environmental Sciences

Background

*Figure 1.* Occurrence of Type I Diabetes in the United States.

*Figure 2.* Deletion of HNF1β gene causes severe pancreatic hypoplasia and decrease in pancreatic weight.

- Diabetes Mellitus is characterized by uncontrolled and elevated blood glucose which is the effect of inadequate levels of plasma insulin.
- Type I Diabetes ultimately stems from the autoimmune destruction of beta cells due to malfunction or lack of the PDX-1 gene.
- The PDX-1 gene is necessary for pancreatic development including the maintenance and survival of β-cells which produce and secrete insulin.
- The HNF1β gene is partially responsible for pancreatic development and lack of this gene can cause pancreatic hypoplasia.

Specific Aim

The specific aim of this study is to determine the relationship between PDX-1 and HNF1β. Comparing these genes to each other and finding potential interactions may reveal essential components in recovering beta-cell function in those with Type I Diabetes.

Potential Pitfalls

- gRNA would not insert properly into the CRISPR-concatemer vector and therefore the gene knockout process would not be successful
- Transfection of the pancreatic islets by means of electroporation would not be successful
- Failure to quantify glucose responsiveness

Potential Conclusions

- After performing this double gene knockout, it is expected to see a significant decrease in beta-cell function and a low amount of quantified glucose responsiveness.
- If the study provides the expected results, a therapy derived from this study would open up lots of new doors for precision medicine and overall improve the quality of life of individuals with Type I Diabetes.

Methodology

1. Split transgenic mice into 4 groups: control, single PDX-1 knockout, single HNF1β knockout, and double knockout
2. Perform single and double gene knockouts of PDX-1 and PDX-1/HNF1β using a CRISPR-concatemer
3. Beta cell performance testing by quantifying the glucose responsiveness

References