Regenerative Medicine and Diabetes

Clinical Outlooks for Regenerative Medicine Metabolic Panel

June 19th, 2012

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Why is diabetes such a problem?

Retinopathy – blindness

Nephropathy – renal failure

Neuropathy – amputation and more

Macrovascular disease – MI and stroke

The key is preventing hyperglycemia
The Diabetes Problem is Enormous and Growing

The cause is not enough insulin-producing cells - pancreatic beta cells. The resulting high blood glucose levels cause the complications.

In type 1 diabetes beta cells are almost entirely wiped out by autoimmunity.

In type 2 diabetes eventually beta cells are reduced to 40-60% of normal.

Replacement of beta cells with transplantation can reverse diabetes.
How might regenerative medicine help?

Replace the missing beta cells

Shut off the autoimmunity that kills beta cells

Slow the progression of vascular disease

Serve as a disease model for both types 1 and 2 diabetes (induced pluripotent stem cells – iPS cells)
Human pancreas: 85 gm
Islet mass: 2%
About one million islets
About one billion beta cells

Courtesy Manami Hara
An Islet

Insulin
Glucagon
Somatostatin

Courtesy Alvin Powers
A Beta Cell

About 10,000 insulin granules

Courtesy Susan Bonner-Weir
Progress with Beta Cell Replacement

1960s: First pancreas transplants

1972: Islet transplants in rats

1980s: Pancreas transplants widespread

1980s: Large animal work with islets

1989: First serious human islet transplants - depressing results

2000: Edmonton Protocol
Proof-of-Principle of Cell Transplantation is Established

- Restores hypoglycemia awareness
- May have a protective effect on long-term diabetic complications
- Improved long-term health-related quality of life after islet transplantation

Where will we find enough beta cells?

Embryonic stem cells
Adult stem/progenitor cells
Beta cell expansion
Genetic engineering
Transdifferentiation - liver, acinar, other
Regeneration
Xenotransplants
Transdifferentiation

Hepatocyte

Acinar Cell

Intestinal Cell

Beta Cell

Genetic and Environmental Manipulation
Factors Contributing to Reprogramming Exocrine Pancreas

1. Islets and exocrine cells appear to originate from the same precursors during fetal development.

2. Pdx1 is needed for pancreas formation and to maintain normal beta cell differentiation.

3. Ngn3 is required for the development of all islet cell types.

4. MafA is required for the latest stage of beta cell maturation (MafB to MafA transition).
Transdifferentiation Acinar to Beta Cells

STZ treatment of rag-1-/-

1 week

M3mCherry

2 weeks

islet transplant under kidney capsule

25 days

virus injected into pancreas

months

removal of islet graft

Assay

Ngn3 P2A Pdx1 T2A Mafa E2A mCherry

CMV

STZ Tpl Virus Nx

Glucose (mg/dl)

0 200 400 600 800

0 4 10 20 30 40 45 50 60 70 80

Time (days)

m3Cherry (n=11-13)
mCherry (n=6-8) untreated Ctrl (n=4)

Courtesy Zhou, Weir, and Melton
Insulitis and Diabetes

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Summary

• Diabetes is a major problem (morbidity, mortality, health care costs)
• The location and geography of the pancreas and the islets pose unique challenges
• Islet transplantation offers proof of principle of cell replacement therapy for diabetes
• Sources of islets
• Overcoming autoimmunity in type 1 diabetes