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RESEARCH NEWS

Pancreatic Beta Cells – The Sweet Life

A review of: Kodama S, Kuhtreiber W, Fuimura S, Dale EA, Faustman DL 2003 Islet regeneration during the reversal of autoimmune diabetes in NOD mice. Science 320:1223–1227; and Ianus A, Holz GG, Theise ND, Hussain MA 2003 In vivo derivation of glucose-competent pancreatic endocrine cells from bone marrow without evidence of cell fusion. J Clin Invest 111:843–850

CHRISTOPHER T. DENNY
PINCHAS COHEN

EVER SINCE THE discovery of insulin 75 years ago, a medical advancement that prevented certain death for type 1 diabetes mellitus (T1DM), the race has been on to "cure" diabetes or at least to free diabetics from the need to receive several daily injections and to be at risk for multiple complications, which together cost the health care systems billions of dollars every year. It has always been assumed that in T1DM, insulin-producing beta cells are for the most part completely destroyed through an autoimmune process. The last several years brought new promise for diabetes in the form of early reports demonstrating efficacy of islet cell transplantations in humans with T1DM as well as a major international effort to develop stem cell-based therapies for diabetes and other diseases. Unfortunately, further assessment of islet cell transplantations indicate that this therapy is unlikely to be available widely and that long-term outcome is not nearly as good as originally hoped. Stem cell research (of both adult and fetal origin) remains an exciting area of research for diabetes, but has yet to translate into a clinically viable therapeutic option in the foreseeable future.

However, recently published data from the Faustman laboratory (1) suggests that even in the T1DM scenario, pancreatic beta cells may be "not dead yet"(2). They have used the Non-obese Diabetic (NOD) mouse strain (a common model of autoimmune T1DM) to demonstrate the regenerative capability of pancreatic beta islet cells in response to immune modulation. In earlier work these investigators demonstrated that administration of normal histo-compatible splenocytes with TNF-alpha, permanently reverted the NOD diabetic phenotype with reappearance of beta islet cells and normal glucose control.

A major unresolved question is whether the new beta cells repopulating the treated mice derive from normal precursors present in the donor splenocyte populations and/or latent stem cells still present in the NOD animals. To address this issue, diabetic female NOD mice were infused with male histo-compatible normal splenocytes along with complete Freund's adjuvant. In addition mice were supported with peri-renal implants of normal beta cells to temporarily maintain glucose homeostasis. After 120 days, beta cell implants were removed and the ability to regulate serum glucose was assessed. In 11 of 12 transplanted mice, normoglycemia was observed for >26 weeks. FISH analysis detecting the Y chromosome demonstrated the presence of male donor cells in the reconstituted pancreatic islets suggesting that splenocyte populations contained competent beta cell precursors. Surprisingly though, transplanting diabetic NOD mice with irradiated normal splenocytes still restored long-term glucose homeostasis, leaving open the possibility that this treatment works as immuno-modulation therapy.

Collectively these data suggested to these investigators that their splenocyte transplant regimen was restoring beta islet cell function by (i) modulating the underlying autoimmunity in the NOD mice and (ii) providing an exogenous source of normal beta cell precursors (or adult stem cell therapy). The latter mechanism may not be entirely necessary since NOD mice transplanted with irradiated cells still reconstituted their pancreatic islets. This suggests that there are endogenous sources of pancreatic beta cells and that future research should focus on the regenerative potential of the patients' own islets.

The recent article from the Hussain laboratory provides further clues where such beta cell precursors may reside (3). These investigators created an indicator mouse strain by crossing a mouse line harboring Cre recombinase under the transcriptional control of the rat insulin promoter, with another strain containing EGFP preceded by three floxed stop codons. Their strategy was that any Cre/EGFP hybrid cells that find their way to the pancreas would transcriptionally up regulate Cre, which would remove the floxed stops and express EGFP. When bone marrow cells from this indicator strain were transplanted into lethally irradiated syn-geneic recipients, this is in fact what happened. Approximately 1-3% of pancreatic islet cells was donor in origin and fluoresced green. These investigators used FACS to sort these cells and found them to have the immunophenotypic profile and cellular responses of functional islet cells.

Further evidence of the potential utility of trophic agents that act to promote islet regeneration and reverse T1DM comes from a series of papers demonstrating that growth factors such as insu-

lin-like growth factor-I (IGF-I) can prevent diabetes in NOD mice. In a recent paper, transgenic expression of IGF-I driven by a beta cell-specific promotor another murine model of T1DM (streptozotocin) completely prevented the appearance of T1DM (4).

Together these discoveries paint a dynamic picture of pancreatic islet cell physiology. Like most mammalian systems, islet cells are likely to have discrete life spans requiring ongoing mechanisms of renewal. What is surprising is that at least in the NOD murine model, type I DM does not appear to be a total wipe out of beta cells but an ongoing autoimmune destructive process. If this process can be halted, NOD mice have the capability to repopulate their beta cell populations from endogenous precursors. These observations in NOD mice could provide new insight into human disease, and refocus clinical research towards a therapeutic approach combining regenerative and immuno-modulatory agents and away from the islet transplantation/stem cell directions.

1. Kodama S, Kuhtreiber W, Fuimura S, Dale EA, Faustman DL 2003 Islet regeneration during the reversal of autoimmune diabetes in NOD mice. Science 320:1223–1227
2. Monty Python and the Holy Grail. Dir. Terry Gilliam and Terry Jones. With Graham Chapman, John Cleese, Eric Idle, Terry Gilliam, Terry Jones and Michael Palin, 1975
3. Ianus A, Holz GG, Theise ND, Hussain MA 2003 In vivo derivation of glucose-competent pancreatic endocrine cells from bone marrow without evidence of cell fusion. J Clin Invest 111:843–850
4. George M, Ayuso E, Casellas A, Costa C, Devedjian JC, Bosch F 2002 Beta cell expression of IGF-I leads to recovery from type 1 diabetes. J Clin Invest 109:1153–1163

Christopher T. Denny
UCLA School of Medicine
Department of Pediatrics
A2-312 MDCC, UCLA Medical Center
Los Angeles,CA 90095
cdenny@ucla.edu

Pinchas Cohen
David Geffen School of Medicine at UCLA
Department of Pediatric Endocrinology
10833 Le Conte Ave., Rm. 22-315 MDCC
Los Angeles, CA 90095
hassy@mednet.ucla.edu
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