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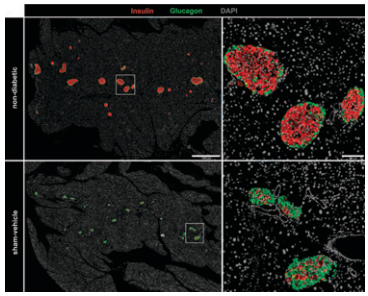
In This Issue of *Diabetes*

Edited by Helaine E. Resnick, PhD, MPH

Islet Transplant Performance in Type 1 Diabetic Mice Improved by Low-Level Leptin Cotherapy

For the treatment of type 1 diabetes, islet transplantation results in improved glycemic control relative to insulin injection, but the paucity of donor islets and decline of graft function over time are barriers to the widespread implementation of this therapy. In this issue of *Diabetes*, research in mice by Denroche et al. (**p. 2738**) shows that effective control of blood glucose can be achieved with a much smaller islet dose if accompanied by low-dose leptin therapy. Using mice with streptozotocin-induced type 1 diabetes and healthy controls, researchers conducted a series of experiments that varied the islet dose—50, 125, or 300 islets (compared to an optimal dose of 300 islets)—and the presence or absence of leptin (1 μg/day, administered via subcutaneous pump). As expected, blood glucose was not significantly lowered in mice receiving only suboptimal islet doses. By contrast, mice receiving 125 islets and leptin maintained glycemic control for the full 40-day study period. At the 125 islet dose, transplant/leptin cotherapy also significantly improved glucose excursions. Plasma insulin concentrations were raised by islet transplantation alone but not by leptin administration alone; because the cotherapy did not further raise insulin levels relative to transplantation without leptin, the authors surmise that, rather than increasing insulin secretion outright, leptin lowers blood glucose by providing a lipid-reducing and more insulin-sensitive environment in which graft-derived insulin can act more effectively. The authors strongly caution against the use of leptin as a monotherapy, noting its decreasing efficacy over time, elevated risk of hypoglycemia, and potential stimulation of β-cell destruction. However, they suggest that the use of low-level leptin cotherapy is a promising approach that warrants further study. — *Wendy Chou, PhD*



Representative images of pancreata from nondiabetic and sham-vehicle groups

Denroche et al. Leptin administration enhances islet transplant performance in diabetic mice. Diabetes 2013;62:2738–2746

Parent-of-Origin Effects and Susceptibility to Type 2 Diabetes in American Indians

Parent-of-origin effects describe cases when gene expression in offspring depends on whether an allele originates maternally or paternally. Recent work on type 2 diabetes has identified a number of single nucleotide polymorphisms (SNPs) that appear to be associated with parent-of-origin effects in some populations in Europe and East Asia. In this issue of *Diabetes*, Hanson et al. (**p. 2984**) report new evidence supporting parent-of-origin effects in Pima Indians, a group with especially high diabetes prevalence. Data on diabetes and associated characteristics were collected longitudinally in 7,351 individuals whose family relationships were also assessed. Genotyping was performed on six SNPs found in *KLF14* (rs4731702), *MOB2* (rs2334499), and *KCNQ1* (rs2237892, rs231362, rs2237895, rs2299620), based on a priori evidence of their association with diabetes. Significant parent-of-origin effects were observed for all six variants, with the strongest effects observed at rs2299620. At this location in *KCNQ1*, there was a nearly 15% increase in diabetes prevalence in carriers of a maternally inherited C allele versus a maternally derived T allele. Further, compared with a maternally inherited T allele, those with a C allele had a 28% reduction in acute insulin secretion. In analyses that were stratified according to likely exposure to a diabetic intrauterine environment, the authors accounted for the potential impact of intrauterine effects on diabetes risk apart from genetic factors. These analyses did not impact their findings. The authors of the new report propose that insulin secretion is subject to imprinting associated with rs2299620. These findings provide new insight into how key variants may increase diabetes risk in specific populations. — *Wendy Chou, PhD*

Hanson et al. Strong parent-of-origin effects in the association of KCNQ1 variants with type 2 diabetes in American Indians. Diabetes 2013;62:2984–2991

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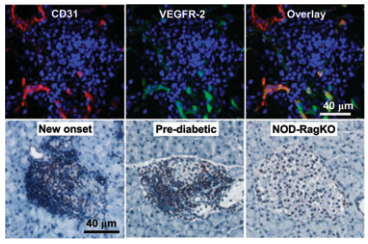
RTKI-Mediated Reversal of Type 1 Diabetes in NOD Mice by VEGFR-2

A cardinal feature of type 1 diabetes (T1D) is damage to pancreatic islets that ultimately results in reduced β-cell mass and hyperglycemia. Improved understanding of the pathways leading to islet cell destruction will offer opportunities to develop new therapeutic targets. In this issue of *Diabetes*, work from Villalta et al. (**p. 2870**) in nonobese diabetic (NOD) mice shows that vascular endothelial growth factor receptor 2 (VEGFR-2) is a central target in the receptor tyrosine kinase inhibitor (RTKI)–mediated reversal of T1D. VEGFR, which has various effects on immunity, vascularization, and cell migration, regulates vasculogenesis and angiogenesis primarily through activation of VEGFR-2. The infiltration of immune cells into the pancreatic islets during the pathogenesis of T1D depends upon activation of VEGFR-2. TKIs have been shown to prevent and reverse diabetes in NOD mice. RTKIs–such as sunitinib–with distinct inhibitory profiles worked more effectively than others in reversing diabetes in this model. VEGFR-2, a target of sunitinib, has been indicated as an important link in regulating the pathogenesis of other inflammatory disorders. In this new work, researchers found that inhibition of VEGFR-2 by RTKIs or blocking antibodies rapidly reversed diabetes. The authors showed impaired T-cell trafficking following VEGFR inhibition. An additional set of experiments demonstrated that the percentage of severely infiltrated islets following treatment with RTKI or anti-VEGFR antibody was significantly reduced compared with vehicle-treated mice. Further, immunologically spared islets and islets with noninvasive insulitis increased in RTKI and antibody-treated mice. When researchers compared tissues from T1D patients and control subjects, insulitis in T1D patients was associated with increased islet vascularity. Taken as a whole, this work indicates that VEGFR-2 antagonists may be useful in the treatment of T1D. — *Laura Gehl, PhD*



Insulitis promotes overexpression of VEGF-A

Villalta et al. Inhibition of VEGFR-2 reverses type 1 diabetes in NOD mice by abrogating insulitis and restoring islet function. Diabetes 2013;62:2870–2878

Upregulation of Adipolin in Krüppel-Like Factor 3–Null Mice

The ongoing epidemic of diet-induced obesity continues to fuel interest in understanding the molecular basis of physiological responses to caloric intake and how these responses can be harnessed to develop therapies to mitigate the metabolic impact of obesity. It is known that various members of the Krüppel-like factor (KLF) family of transcription factors have been implicated in adipogenesis. KLF3 is known to inhibit adipogenesis, and *Fam132a* is a KLF3 target gene. The absence of KLF3 leads to upregulation of the adipokine adipolin, which has been shown to improve glucose tolerance and insulin sensitivity in mouse models of obesity and diabetes. In this issue of *Diabetes*, Bell-Anderson et al. (**p. 2728**) demonstrate an in vivo interaction between KLF3 and the Fam132a promoter. In KLF3-null mice, the researchers found upregulation of *Fam132a* mRNA expression and plasma adipolin levels. They confirmed that KLF binds and represses the *Fam132a* promoter in vitro and verified a direct interaction between KLF3 and the *Fam132a* promoter in vivo. KLF3-null mice, which are lean and have disrupted adipogenesis, had reduced adipocyte size and number. In vivo experiments with these mice revealed a reduction in both subcutaneous and visceral white adipose tissue depots. $KLF3^{-/-}$ mice fed a high-fat diet demonstrated no observable change in food intake or energy expenditure but remained significantly lighter than $KLF3^{+/+}$ or $KLF3^{+/-}$ littermates. Further, $KLF3^{-/-}$ mice had better glucose tolerance than wild-type mice. Circulating plasma adipolin was elevated on chow and high-fat diets in the absence of KLF3. Collectively, these results indicate that KLF3 is a regulator of *Fam132a*, the gene coding for the insulin-sensitizing factor adipolin. Targeting KLF3 as a means of boosting adipolin levels may offer a new strategy for treating insulin resistance. — *Laura Gehl, PhD*

Bell-Anderson et al. Loss of Krüppel-like factor 3 leads to upregulation of the insulin-sensitizing factor adipolin. Diabetes 2013;62:2728–2737

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