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In This Issue of *Diabetes*

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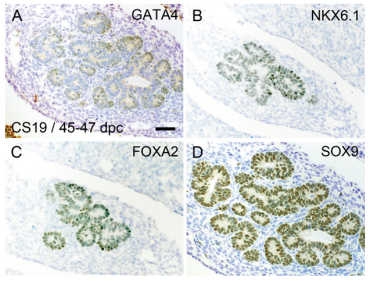
A Detailed Look at the Early Stages of Embryonic Development of the Human Pancreas

Work by Jennings et al. (**p. 3514**) presented in this issue of *Diabetes* helps to address the basic need for data on human pancreatic development during the late embryonic and early fetal stages. Logistical and ethical restrictions associated with obtaining human tissue prior to 7–8 weeks of age have hindered the ability of researchers to determine whether early endocrine development in humans parallels the pathways found in more well-studied mouse models. In this new study, investigators performed immunohistochemical analyses on 31 human embryo and fetal specimens ranging from 47 days postconception to 10 weeks postconception and catalogued the transcription factors expressed at each developmental stage. With a focus on major contrasts between humans and mice, the results showed that while mouse embryos typically express the factor Neurogenin3 (NEUROG3, a hallmark of endocrine commitment) in two phases, NEUROG3 expression in human embryos occurred in a single wave beginning at 8–10 weeks postconception. Along with the increase in NEUROG3 expression, the investigators detected the factor NKX2.2 only at the time of human fetal β-cell differentiation, whereas NKX2.2 is a multipotent pancreatic progenitor in mouse embryos. By identifying combinations of transcription factors marking the stages of pancreatic development and underscoring key differences in humans, these new data help advance the long-term goal of developing novel therapies for diabetes, including the generation of β-cells from pluripotent stem cells. — *Wendy Chou, PhD*



Sections through the pancreas of a human embryo at 45–47 days post-conception (dpc) and stained with toluidine blue after immunohistochemistry (brown) for GATA4 (*A*), NKX6.1 (*B*), FOXA2 (*C*), and SOX9 (*D*)

Jennings et al. Development of the human pancreas from foregut to endocrine commitment. Diabetes 2013;62:3514–3522

ADAMTS13 Variant Pro618Ala Increases Risk of Renal and Cardiovascular Disease in Type 2 Diabetes

A new study by Rurali et al. (**p. 3599**) contributes to a growing body of literature suggesting that pharmacogenetics may play an increasing role in identifying therapeutic strategies that are tailored to the needs of individual patients. Type 2 diabetes increases the risk for cardiovascular disease and microvascular complications such as nephropathy, retinopathy, and neuropathy. Two factors known to play an important role in the pathogenesis of these complications are endothelial cell dysfunction and uncontrolled platelet activation. The multimeric glycoprotein von Willebrand factor (VWF), stored as highly thrombogenic ultralarge multimers (ULVWF), is thought to be involved in the excess platelet activation observed in type 2 diabetes. The cleavage of ULVWF by the plasma metalloprotease ADAMTS13 is necessary for modulating the thrombotic process. A lack of ADAMTS13 may lead to uncontrolled VWF-mediated thrombosis, and low ADAMTS13 levels have been associated with renal and cardiovascular events in diabetic and nondiabetic patients. In this issue of *Diabetes*, Rurali et al. investigate Pro618Ala, one of several ADAMTS13 single nucleotide polymorphisms. Previous studies suggest that patients carrying the 618Ala variant have reduced ADAMTS13 activity and thus may be at greater risk for renal and cardiovascular disease. In the new research presented by Rurali et al., the investigators hypothesized that diabetes-associated endothelial dysfunction leading to a reduction of ADAMTS13 activity would be more likely to result in renal or cardiovascular complications in patients with the Pro618Ala genotype. They genotyped 1,163 normoalbuminuric patients with type 2 diabetes in the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) who were randomized to receive the ACE inhibitor (ACEi) trandolapril or non-ACEi therapy. Carriers of the 618Ala variant were found to have the highest risk of cardiac and renal events, and they also showed the most benefit from ACEi therapy. These results suggest that ACEi therapy increases ADAMTS13 bioavailability and decreases the prothrombotic effects of ULVWF multimers. In the future, information on genetic factors that can enhance or hinder the impact of specific therapies may help support clinical decision-making. — *Laura Gehl, PhD*

Rurali et al. ADAMTS13 predicts renal and cardiovascular events in type 2 diabetic patients and response to therapy. Diabetes 2013;62:3599–3609

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Pravastatin and Valsartan Combination Therapy Has Synergistic Effects in Hypercholesterolemic Patients

New data presented in this issue of *Diabetes* (**p. 3547**) are the first to show that combination therapy with a statin and valsartan result in simultaneous improvements in endothelial function, inflammatory markers, adiponectin, and insulin resistance—all to a greater extent than with monotherapy. Hypercholesterolemia and hypertension are often associated with obesity and type 2 diabetes. While statin therapy reduces coronary risk and atherosclerosis, statins such as simvastatin and rosuvastatin may enhance glucose dysregulation. The new study by Koh et al. hypothesizes that a combination of pravastatin plus valsartan in hypercholesterolemic patients could result in simultaneous, additive benefits to both endothelial and metabolic phenotypes. In a randomized, single-blind, placebo-controlled trial, 48 hypercholesterolemic patients, 23 of whom also had metabolic syndrome, were given 40 mg pravastatin and placebo, 160 mg valsartan and placebo, or 40 mg pravastatin and 160 mg valsartan daily for 2 months. Combination therapy did not result in synergistic effects for either blood pressure or lipids. In contrast, and relative to monotherapy, pravastatin plus valsartan resulted in better brachial artery flow–mediated dilation, greater reductions in C-reactive protein, increased plasma adiponectin, and lower fasting insulin levels. Although the investigators caution that pravastatin has some limitations, they point out that this statin does not cause worsening of glucose regulation and may therefore be of particular interest in managing cardiovascular risk in people with diabetes. — *Laura Gehl, PhD*

Koh et al. Combination pravastatin and valsartan treatment has additive beneficial effects to simultaneously improve both metabolic and cardiovascular phenotypes beyond that of monotherapy with either drug in patients with primary hypercholesterolemia. Diabetes 2013;62:3547–3552

Favorable Impact of Resveratrol Supplementation on β-Cell Morphology and Transcription Factors in Monkeys

The possibility that adding resveratrol to a diet high in fat and sugar—a dietary pattern commonly associated with the development of type 2 diabetes—may protect β-cell morphology and function from some of the diet's deleterious effects is the focus of an article in this issue of *Diabetes* (**p. 3500**). In rodent models of type 2 diabetes, resveratrol has been shown to protect β-cells and improve insulin action, but pathology in humans is better represented by primate models in which resveratrol's effects remain poorly understood. Fiori et al. randomized adult rhesus monkeys to a standard diet (SD; $n = 4$), a high-fat/high-sugar diet plus placebo (HFS; $n = 10$), or a high-fat/high-sugar diet plus up to 480 mg of oral resveratrol daily ($n = 10$). At 24 months, the HFS group weighed significantly more, had elevated insulin area under the curve, and exhibited greater insulin resistance relative to the SD group, although the HFS group did not show overt dysglycemia. These metabolic shifts were also observed in monkeys on the HFS diet plus resveratrol. However, adding resveratrol to the HFS diet appeared to prevent key changes to islet morphology. Pancreata of HFS monkeys had decreased β-cells and increased α-cells, whereas the resveratrol-supplemented group maintained normal ratios of α-cells to β-cells that were similar to the SD group. Furthermore, the HFS diet was linked to decreased signaling of the tyrosine-phosphorylated insulin receptor (P-IR) and to the depletion of β-cell–specific transcription factors (FOXO1, NKX6-1, NKX2-2, and PDX1), but resveratrol supplementation protected β-cells from P-IR signaling and transcription factor losses. As neither apoptosis of β-cells nor mitosis of α-cells were detected, the investigators hypothesized that β-cells dedifferentiated and may have become α-cells, an idea that could explain why islet size was unchanged. Additional experiments involving incubation of human islets under HFS-like conditions (high glucose and sodium palmitate) and selective Sirtuin 1 (SIRT1) inhibition resulted in a significant decrease in insulin secretion suggesting that resveratrol's effects on insulin secretion are mediated through SIRT1. Blocking SIRT1 in human islets also prevented upregulation of β-cell transcription factors. The new findings suggest that resveratrol supplementation may be a cost-effective means to protect β-cells in individuals who are at risk of developing type 2 diabetes. — *Wendy Chou, PhD*

Fiori et al. Resveratrol prevents β-cell dedifferentiation in nonhuman primates given a high-fat/high-sugar diet. Diabetes 2013;62:3500–3513

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