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Highlights From the Latest in Diabetes Research

Significant Progress in Somatic Cell Nuclear Transfer

Pluripotent embryonic stem cells (ESCs) may be generated by reprogramming somatic cells through transplantation of the somatic cell nucleus into an enucleated donor oocyte, a method referred to as somatic cell nuclear transplant (SCNT). Although this method has been successful in generating nuclear transfer-ESCs (NT-ESCs) in a variety of mammalian species, early embryonic arrest (prior to formation of the blastocyst) has prevented derivation of stable *human* NT-ESCs. Through systematic evaluation of the SCNT protocol, Tachibana et al. identified key factors limiting its success (i.e., early exit of the oocyte from meiosis and inadequate cytoplast activation posttransplant) and optimized the approach to successfully derive the first human NT-ESCs. The authors tweaked the protocol to ensure transplant into meiotically active cytoplasts, used electroporation to improve cytoplast activation, and added caffeine during enucleation and fusion to facilitate blastocyst development. They also determined that using high-quality donor oocytes (as opposed to leftover oocytes from in vitro fertilization procedures) improved ESC derivation efficiency and yield. This breakthrough in reprogramming somatic cells into pluripotent ESCs provides the opportunity to further our understanding of biological systems and disease mechanisms. Creating cells, tissues, and organs genetically identical to a patient's somatic cells will allow researchers to dissect the effects of gene mutations and other perturbations in tissues not easily accessible for biopsy, including liver, pancreas, and heart. Ultimately, this may help develop cell/organ transplant therapies such as neuronal cells for Alzheimer and Parkinson diseases, β-cells for diabetes, and whole organs for transplant. — *Coleen M. Damcott, PhD*

■ Tachibana et al. Human embryonic stem cells derived by somatic cell nuclear transfer. Cell 2013;153:1228–1238

Fractalkine: A New Player in the Regulation of β-Cell Function

Fractalkine (FKN) is a chemokine that is expressed in diverse cell types. By binding to its receptor CX3CR1 (which is also known as GPR13), FKN mediates cell-to-cell adhesion and communication in hepatocytes, neurons, and other cells. FKN modulates monocyte attachment to adipocytes and some of its single nucleotide polymorphisms have been associated with an increased incidence of metabolic syndrome and type 2 diabetes. However, the role of FKN in control of pancreatic function had not been well defined. A new study by Lee et al. describes a novel function of the FKN/CX3CR1 system in modulation of β-cell insulin secretory function. The investigators observed that, compared with their wild-type (WT) counterparts, lean and diet-induced obese mice in which the CX3CR1 gene was knocked out (KO) developed glucose intolerance and displayed decreased insulin and C-peptide secretion in response to oral and intravenous glucose challenges as well as arginine stimulation. Consistent with this observation, anti-FKN antibody administration led to decreased C-peptide levels and impaired glucose tolerance. Further, isolated islets from KO mice produced less insulin in response to high glucose and glucagon-like peptide 1 stimulation, and they also had decreased expression of genes associated with β-cell function. These defects were restored toward normal by in vitro FKN treatment. FKN administration in WT mice also led to improvement in insulin secretion and glucose tolerance. Collectively, these data demonstrate that the β-cell FKN/CX3CR1 system is necessary for normal insulin secretory function in response to glucose, arginine, and glucagon-like peptide 1, both in vitro and in vivo. Looking forward, a FKN-based therapeutic or a small-molecule CX3CR1 agonist may be added as exciting new tools to combat type 2 diabetes. — *Jenny Tong, MD, MPH*

■ Lee et al. The fractalkine/CX3CR1 system regulates β cell function and insulin secretion. Cell 2013;153:413–425

Mechanisms Underlying the Effects of GLP-1 on Blood Pressure Elucidated

Patients with type 2 diabetes frequently experience comorbid conditions such as hypertension and kidney disease that contribute to the challenges of effective patient management. The complexity of these patients implies that therapies offering beneficial effects for metabolic disturbances other than elevated glucose have the potential to be of particular value. It has been shown that glucagon-like peptide 1 (GLP-1) receptor agonists, a new class of glucose-lowering drugs, have beneficial impacts beyond promoting glycemic control. These drugs stimulate satiety, reduce postprandial lipemia, and they have also been shown to reduce blood pressure. The high prevalence of hypertension among type 2 diabetic patients underscores the importance of understanding the mechanisms through which GLP-1 receptor agonists exert their antihypertensive effects in this patient population. New research by Kim et al. highlights a critical role for atrial natriuretic peptide (ANP) as a mediator of GLP-1's favorable effects on blood pressure. The new report demonstrates that the antihypertensive action of GLP-1 receptor agonists is attributable to natriuresis and vasodilation via the release of ANP. It suggests a critical link between GLP-1 released from the gut and ANP, highlighting a

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potentially important role for the GLP-1–ANP gut-heart axis in influencing cardiovascular risk in diabetes. Understanding the mechanistic basis of the pleiotropic effects of GLP-1 receptor agonists is of particular relevance as the population ages and common chronic conditions such as diabetes and hypertension continue to rise. — *Helaine E. Resnick, PhD, MPH*

- Kim et al. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. Nat Med 2013;19:567–575

When Reshaping the Silhouette Remodels DNA

Gastric bypass surgery is not only one of the most effective means to induce rapid weight loss in obese patients, it also has dramatic effects on glycemic control in type 2 diabetes. Interestingly, although obese patients with type 2 diabetes who undergo this procedure often experience improvements in glucose regulation, the mechanisms underpinning this relationship are not well understood. A new study by Swedish investigators provides insight into how this might occur. The study shows that obesity is associated with modifications in genes that are involved in lipid metabolism and energy expenditure and that weight loss induced by gastric bypass surgery normalized expression of these important genes. In particular, Barres et al. identified two genes—PGC-1α and PDK4—for which changes in DNA methylation (the chemical marks on the genome that control gene expression in response to environmental factors) take place in obesity and are restored to normal after weight loss. From a therapeutic standpoint, this study suggests that the development of drugs that aim to mimic these weight loss–associated DNA alterations could be of potential interest for the treatment of both obesity and the metabolic alterations that accompany it. — *Nathalie Fiaschi-Taesch, PhD*

- Barres et al. Weight loss after gastric bypass surgery in human obesity remodels promoter methylation. Cell Rep 2013;3:1020–1027

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