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Highlights From the Latest in Diabetes Research

Enhanced CHD Risk in Diabetes: New Insight Into the Genetics of Glutamic Acid Metabolism

Although it has been known for some time that genetic factors can act to enhance the risk for coronary heart disease (CHD), it has been less clear why these factors often show a differential impact among diabetic and nondiabetic individuals. As the prevalence of diabetes continues to increase worldwide, improved understanding of the mechanisms underpinning the impact of specific genes on CHD risk in diabetes might offer new opportunities for interventions that target specific mechanisms of glucose metabolism among high-risk diabetic individuals. A new report by Qi et al. used data from five large cohort studies and showed that rs10911021, a variant on chromosome 1q25 that is functionally related to glutamic acid metabolism, may be a genetic factor that acts to enhance CHD risk in the presence of diabetes, but not when diabetes is absent. The report used a three-stage approach to examine the impact of this variant on the odds of CHD among diabetic case subjects and control subjects across the cohorts. Among diabetic individuals, there was a significant association between rs10911021 and odds of CHD (odds ratio [OR] = 1.36, 95% CI 1.22–1.51) but this association was absent among nondiabetic individuals from the same studies (OR = 0.99, 95% CI 0.87–1.13). The differential impact of the variant suggests that it interacts with diabetes to enhance CHD risk. Further investigation of protective and risk-enhancing alleles in human endothelial cells showed a nearly one-third reduction in the expression of the glutamate-ammonia ligase (*GLUL*) gene, as well as a lower ratio of pyroglutamic and glutamic acid. When the decreased ratio of these γ-glutamyl cycle intermediates was considered in statistical models that quantified the odds of CHD associated with the risk allele homozygotes, the odds decreased, suggesting that this factor was partly responsible for the enhanced CHD risk associated with the risk alleles. These findings indicate that among diabetic individuals, rs10911021 may increase CHD risk by disrupting the γ-glutamyl cycle, a finding that may lead the way to the identification of therapies tailored to the needs of diabetic individuals. — *Helaine E. Resnick, PhD, MPH*

■ Qi et al. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. JAMA 2013;310:821–828

Impact of the "Other Genome" on Adiposity and Metabolism

As the obesity epidemic continues to spread in both developed and developing countries, novel approaches to understanding obesity risk factors may pave the way for the development of innovative therapies. Although personalized medicine—including the use of genetic information to tailor health care provisions to individual patient needs—has long been considered in the context of obesity, it is also clear that genetic factors explain only a very small proportion of the variability in common indices of obesity such as BMI. A new report based on data from 123 nonobese and 169 obese Danish individuals focuses on the "other genome"—the gut microbiome. The investigators hypothesized that genetic variation in the microorganisms that inhabit the human gut may help explain differences in both obesity and metabolic markers that are often associated with obesity. They first noted that the number of bacterial genes in their study sample followed a bimodal distribution; based on this observation, they defined two groups based on the number bacterial genes. Participants with less than 480,000 genes were categorized as having a "low" gene count, and the rest of the sample was defined as having a high gene count. The number of bacterial genes in the two groups differed by 40%, suggesting that some individuals have a considerably richer microbiota than others. In this study sample, 23% of participants had low bacterial richness. When compared to their counterparts with a richer gut microbiome, those with low bacterial richness were heavier, more insulin resistant, and dyslipidemic. Further analyses of specific bacterial genes that distinguished lean from obese individuals suggested that obesity-related signals from a relatively small number of bacterial genes in the human gut microbiome may be stronger than signals from the human genome. These results suggest the notion that diagnostic testing for specific microorganisms may help in the stratification of obesity risk. — *Helaine E. Resnick, PhD, MPH*

■ Le Chatelier et al. Richness of human gut microbiome correlates with metabolic markers. Nature 2013;500:541–546

β1-Integrin Is Required for β-Cell Proliferation

The α-integrins directly bind components of the extracellular matrix (ECM) and heterodimerize with β-integrins to initiate intracellular signaling pathways that are critical for cell adhesion, migration, proliferation, cell survival, and differentiation. A recent article by Diaferia et al. found that β-cell–specific deletion of β1-integrins in mice impaired β-cell proliferation during late embryogenesis and continued through postnatal development, leading to smaller islets containing an 82% reduction in β-cells. Surprisingly, the few remaining β-cells in the β-cell–specific β1-integrin knockout mice appeared phenotypically normal and were able to physiologically compensate for the depletion in their overall number by augmenting their insulin secretion to maintain blood glucose levels at normal levels. Analysis of cultured β1-integrin–deficient β-cells revealed defects in ECM adhesion to collagen IV and fibronectin, impaired proliferation, and reduced integrin signaling, including the activation Erk, Akt, and PTEN. Transcriptome analysis revealed β1-integrin–deficient β-cells also had abnormal expression of several cell adhesion and cell cycle genes. Collectively, these results demonstrate that β1-integrin is specifically required for β-cell proliferation in vivo and may therefore be useful as a therapeutic target for expanding β-cells in diabetic patients or in β-cells cultured for transplantation. — *Anthony Romer, PhD*

■ Diaferia et al. β1-integrin is a crucial regulator of pancreatic β-cell expansion. Development 2013;140:3360–3372

Maturing Stem Cell Analyses With MODY2 Subjects

Central to virtually all forms of diabetes is reduced β-cell mass and/or β-cell function. It is known that human stem cells, both embryonic and inducible pluripotent stem cells (iPSCs), can differentiate into β-cells. Of new interest is whether β-cells generated from iPSCs from patients with various forms of diabetes could advance the understanding and treatment of β-cell dysfunction. A necessity, however, to using iPSC-derived β-cells to advance β-cell therapy is validation of whether these cells maintain their subject's phenotype. Recent work by Hua et al. took advantage of the characteristic features of maturity-onset diabetes of the young type 2 (MODY2) to assess the accuracy of modeling diabetes with iPSCs. In MODY2, a monogenic form of diabetes, a mutation in the glucokinase (*GCK*) gene, impairs glucose-stimulated insulin secretion. Hypofunction of one allele of GCK suppresses the catalytic conversion of glucose to glucose-6-phosphate, a reaction that serves as a glucose sensor for the β-cell. The investigative team of Hua et al. obtained skin biopsies from two MODY2 subjects. The *GCK* gene from both patients carried different missense mutations, which have been shown to be functionally hypomorphic with less than 1% of activity of the wild-type allele. Design of an innovative two-step targeting protocol allowed the precise correction of the mutant base pair, without leaving a footprint of exogenous DNA. These targeted manipulations generated an allelic series of cells that were wild-type, hypomorphic, or null for GCK function on the same genetic background. A stepwise differentiation of these iPSCs in vitro—and then in vivo—resulted in comparable mature β-cells. Measures of human C-peptide concentrations in mouse sera displayed characteristics of healthy, glucose-responsive or diabetic, glucose-unresponsive β-cells. Consistent with MODY2 displaying GCK mutations specifically affecting glucose-mediated insulin secretion, C-peptide secretion from wild-type, hypomorphic, or null GCK cells was similarly stimulated when exposed to other secretagogues not dependent of GCK activity such as arginine, potassium, and calcium channel agonists. These data elegantly show efficient iPSC-generated β-cells that replicate a pathologic phenotype. In combination with gene correction, these findings further illustrate a novel therapeutic strategy for cell replacement to restore normal glucose homeostasis. — *Jeffrey S. Elmendorf, PhD*

■ Hua et al. iPSC-derived β cells model diabetes due to glucokinase deficiency. J Clin Invest 2013;123:3146–3153

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