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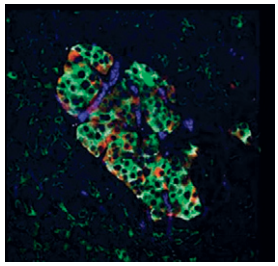
In This Issue of *Diabetes*

Edited by Helaine E. Resnick, PhD, MPH

New Autoantibodies Help Predict Type 1 Diabetes

Newly identified autoantibodies may help in the screening and diagnosis of type 1 diabetes. Although autoantibodies such as GAD65, ICA, and IA-2 are associated with increased risk of type 1 diabetes, none of these is universally present in type 1 diabetic patients, and even combinations of these autoantibodies do not predict type 1 diabetes onset with certainty. The absence of reliable immunologic markers for the screening and diagnosis of type 1 diabetes not only hinders efforts to identify high-risk individuals prior to disease onset, but it also impedes understanding of the various mechanisms that underpin β-cell destruction in these patients. This issue of *Diabetes* features findings on two new autoantibodies that are strongly associated with type 1 diabetes (**p. 3022**). The new report summarizes findings from studies in which serum samples from patients with type 1 diabetes and type 2 diabetes and normal glucose tolerant patients were profiled with protein microarrays containing nearly 9,500 proteins. This work led to the identification of two autoantibodies—anti-EEF1A1 and anti-UBE2L3—that were expressed more abundantly in the type 1 diabetic patients relative to the other groups. To validate these findings, the abundance of these autoantibodies was examined in two separate cohorts that contained a mix of patients including people with type 1 diabetes, type 2 diabetes, latent autoimmune diabetes of adults, Graves disease, and people with normal glucose tolerance. The validation studies not only confirmed that anti-EEF1A1 and anti-UBE2L3 were significantly more abundant in type 1 diabetic patients, but the data also showed that more than 40% of GAD-negative patients were positive for one or both of the newly identified autoantibodies. In fact, the new autoantibodies increased the proportion of type 1 diabetic patients with evidence of autoimmunity from 76.3 to 86%. These intriguing new findings suggest that there may be new tools on the horizon that can help improve the screening and diagnosis of type 1 diabetes. — *Helaine E. Resnick, PhD, MPH*



Localization of candidate autoantigens in pancreatic β-cells.

Koo et al. Identification of novel autoantibodies in type 1 diabetic patients using a high-density protein microarray. Diabetes 2014;63:3022–3032

Stem Cell Therapy in Type 1 Diabetes Has Beneficial Effects (and Safety Concerns)

Hematopoietic stem cell (HSC)–based therapy for type 1 diabetes appears to be a promising strategy, but it still has a long way to go to ensure safety. This issue of *Diabetes* contains long-term follow-up data from three clinical trials in which patients with new-onset type 1 diabetes received a novel HSC-based therapy (**p. 3041**). The pooled data from these studies—one conducted in Poland and the other two in China—showed promising results for the HSC therapy over 48 months of follow-up. At 6 months, 59% of patients were insulin independent, and 32% retained this independence at the last follow-up. Further, HbA_{1c} decreased and C-peptide increased. These findings showcase both improved glycemic control and β-cell function among treated patients. The investigators noted that relative to those who responded more favorably to treatment, poor responders were younger at enrollment, had higher A1C, and were enrolled in the study at a later point after diabetes diagnosis. The striking results from the pooled data were mitigated by significant safety concerns: 53% of the patients had adverse events. The most common side effects were neutropenic fever, alopecia with fever, gastrointestinal symptoms, and severe infectious disease—including one patient who died from *Pseudomonas aeruginosa*. Although the data in the new report are the first to demonstrate remission of type 1 diabetes among early-onset patients, the authors stress that more work is needed and that this therapy may ultimately be suitable for only a subset of patients. — *Helaine E. Resnick, PhD, MPH*

D'Addio et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in new-onset type 1 diabetes: a multicenter analysis. Diabetes 2014;63:3041–3046

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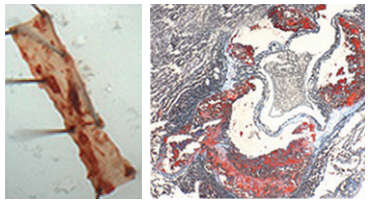
Genetic and Epigenetic Profiling Yields Novel Findings Among Discordant Twins

This issue of *Diabetes* includes intriguing data that provide new insight into the relative contributions of genetics and environment to diabetes risk (**p. 2962**). Nilsson et al. sampled adipose tissue from pairs of monozygotic twins that were discordant for type 2 diabetes. mRNA was extracted from these samples in work that focused on whether specific genes were differentially expressed in the twin sets. This strategy controlled for the effects of genotype, sex, and age, thereby allowing a better understanding of the potential impact of nonshared environmental factors. Compared to their nondiabetic counterparts, the diabetic twins' profiles revealed marked downregulation of gene sets involved in amino acid, carbohydrate, and lipid metabolism. The diabetic twins also exhibited greater upregulation of genes that are linked to inflammation and glycan degradation. Notably, *SPP1*, the most overexpressed gene among the affected twins, encodes osteopontin, an inflammatory cytokine that is linked to insulin resistance as well as a number of chronic inflammatory conditions. Six of the genes that showed the greatest contrasts among the twins were further analyzed in a cohort of unrelated patients to validate the initial findings. The validation data confirmed earlier patterns of differential gene expression, thereby adding evidence to the clinical relevance of the findings. Because type 2 diabetes is associated with environmental risk factors like diet and exercise, the work also examined the potential role of epigenetic markers in relation to the twins' RNA expression data set. With a focus on patterns in DNA methylation, these findings revealed that among the discordant twins, relatedness between each pair of twins far outweighed any similarities shared by the diabetic individuals as a group, an observation suggesting an influence of heritability for methylation changes. As a whole, the new report suggests that a multitude of both transcriptional and epigenetic changes that are associated with the development of diabetes are present in the adipose tissue of diabetic individuals. — *Wendy Chou, PhD*

Nilsson et al. Altered DNA methylation and differential expression of genes influencing metabolism and inflammation in adipose tissue from subjects with type 2 diabetes. Diabetes 2014;63:2962–2976

Low Dose of an Orally Administered Antioxidant Inflammation Modulator Reduces Diabetes-Associated Damage to Heart and Kidney

A new report by Tan et al. in this issue of *Diabetes* (**p. 3091**) offers evidence for a reduction in both renal and cardiac complications in diabetic mice that received low doses of dh404, an antioxidant inflammation modulator (AIM). This AIM is of interest because it is an analogue of bardoxolone methyl (BM), another AIM that showed promise in recent years as a treatment for advanced kidney disease. However, phase 3 BM trials were terminated abruptly because of concerns over unexplained cardiovascular events. Nonetheless, the demand for therapies that can reduce the renal and cardiac complications of type 2 diabetes is pressing, a consideration that motivated the current study in which dh404 was tested as a surrogate for BM. The rationale for this approach was that dh404 might potentially avoid the undesirable off-target and toxic effects associated with BM, thereby providing insight into the pharmacokinetics of this promising therapy. Diabetic mice received 0, 3, 10, or 20 mg/kg dh404 for 18 weeks, and nondiabetic controls received either 0 or 10 mg/kg dh404. Increases in total atherosclerotic plaque and aortic sinus lesions in diabetic mice were both significantly attenuated at the 3 and 10 mg/kg treatment levels, but higher doses offered no benefit. Similar improvements were also observed in renal function. All levels of dh404 reduced urinary albumin-to-creatinine ratio. However, only the lowest dh404 dose reduced mesangial expansion in glomeruli, and this dose resulted in the greatest attenuation of tubulointerstitial injury. In vitro experiments suggested that the lack of end-organ protection at higher doses may be due to off-target effects of the drug. These data showed significant dose-dependent upregulation of MCP-1 in normal rat kidney cells, an observation suggesting increased inflammation at higher doses. Further investigation of dosage requirements in the preclinical setting should help determine whether these compounds can offer a useful therapeutic option to reduce diabetic vascular complications. — *Wendy Chou, PhD*



Diabetes-associated lesion formation in the aorta (*left*) and aortic sinus (*right*).

Tan et al. Derivative of bardoxolone methyl, dh404, in an inverse dose-dependent manner, lessens diabetes-associated atherosclerosis and improves diabetic kidney disease. Diabetes 2014;63:3091–3103

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