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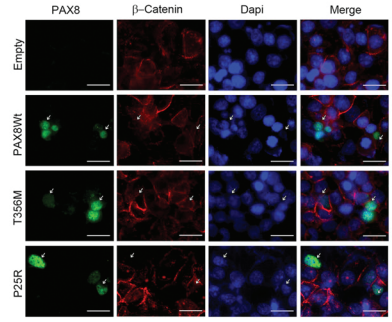
In This Issue of *Diabetes*

By Max Bingham, PhD

PAX8 Expression in Islets During Pregnancy and Gestational Diabetes Mellitus

According to Martin-Montalvo et al. (**p. 109**), increased but transient expression of *PAX8* appears to improve islet survival in pregnancy and might therefore represent a candidate gene for dealing with gestational diabetes mellitus (GDM). More specifically, it seems that mutations on PAX8 can be linked to GDM, with the authors describing individuals with novel mutations who went on to develop GDM. The findings come from a series of experiments involving cells from various mouse models and human islets in which the expression of *PAX8* was investigated. Further studies were also undertaken with pregnant women who agreed to undergo genetic screening and sequencing of the *PAX8* gene. They found that *Pax8* was induced in islets from gestating mice and in human islets exposed to conditions mimicking pregnancy. Global gene expression analysis of both human and mouse islets that were overexpressing the relevant *PAX8* revealed genetic pathways that were active and seemed to converge on cell survival. The authors also show that apoptosis was reduced in cells overexpressing *PAX8*, implying that *PAX8* plays a role in cell survival. They go on to genotype a series of patients with GDM and gestational thyroid dysfunction, which is commonly associated with *PAX8* mutations, identifying two novel missense mutations that were also present in family members but absent in control subjects. Authors Benoit R. Gauthier, Alejandro Martin-Montalvo, and José Carlos Moreno told *Diabetes*: "To date the pathogenesis of GDM still remains unknown. Here, we reveal that functional mutations within the *PAX8* gene are found in patients with GDM, opening the prospect of a new genetic tool for the diagnosis and prediction of GDM. In this context, we are eager to follow up on three young female patients bearing these *PAX8* gene mutations in order to assess the impact during pregnancy. Our study certainly warrants the screening of larger cohorts of women with GDM for the identification of mutations in *PAX8* or in other genes involved in the β-cell survival/plasticity pathway in the future."

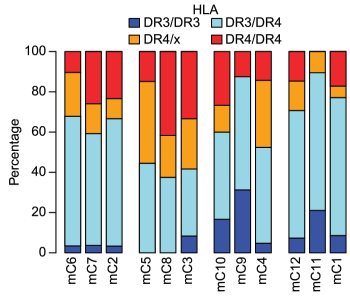


The PAX8-T356M and PAX8-P25R mutations are found in two patients who developed GDM, and both mutations exhibit compromised transcriptional activity. Representative immunofluorescence images depicting normal subcellular localization of the different PAX8 variants. Scale bars = 25 μm.

Martin-Montalvo et al. Transient *PAX8* expression in islets during pregnancy correlates with β-cell survival, revealing a novel candidate gene in gestational diabetes mellitus. Diabetes 2019;68:109–118

Autoimmunity Profiling Helps Stratify Preclinical Type 1 Diabetes

The relationship between the appearance of β-cell autoantibodies and the transition to type 1 diabetes is examined by Endesfelder et al. (**p. 119**), revealing that it is possible to cluster individuals on the basis of the longitudinal appearance of single or multiple autoantibodies and that this stratified risk of progression to clinical diabetes within 5 years. The findings come from an investigation of 600 children enrolled in The Environmental Determinants of Diabetes in the Young (TEDDY) birth cohort study who developed one or more persistent autoantibodies toward β-cells. These were insulin autoantibodies (IAA), insulinoma-associated antigen 2 autoantibodies (IA-2A), and GAD autoantibodies (GADA). The children were then followed up at 3- to 6-month intervals to track the development of the autoantibodies and whether the individuals transitioned to type 1 diabetes. The authors found that it was possible to cluster individuals according antibody status and age at seroconversion and found that 12 clusters of individuals emerged with multiple autoantibodies. Notably, the percentage of individuals varied considerably in each of the clusters that transitioned to clinical diabetes, ranging from 6% to 84% within 5 years. A complex picture then emerges of the characteristics of the clusters. The authors highlight that children who seroconverted very early (i.e., aged <2 years) and specifically developed IAA and IA-2A that remained stable positive on follow-up had the highest risk for diabetes. They go on to suggest that their approach and clustering can be used for more refined explorative research into the underlying mechanisms relating to β-cell autoimmunity and thus the development of type 1 diabetes. Author Peter Achenbach said: "The varying temporal patterns in autoantibody development reveal striking differences in what, up to now, has been considered simply as multiple-autoantibody positivity. The new approach therefore provides a significant step forward toward a refined phenotyping of β-cell autoimmunity and a tool in the search for etiological factors."



The proportions HLA-DR genotypes among the children in the multiple-autoantibody clusters (mC1–mC12). The group comprising mC5, mC8, and mC3 had a lower frequency of HLA-DR3 than did the other cluster groups.

Endesfelder et al. Time-resolved autoantibody profiling facilitates stratification of preclinical type 1 diabetes in children. Diabetes 2019;68:119–130

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IGFBP-2 Plasma Levels Linked to Type 2 Diabetes Risk

Circulating levels of insulin-like growth factor binding protein 2 (IGFBP-2) appear to predict risk of developing type 2 diabetes, according to Wittenbecher et al. (**p. 188**). Specifically, higher levels of IGFBP-2 appear to protect against developing type 2 diabetes, and it seems that silencing the gene for IGFBP-2 via DNA methylation is also linked with risk levels for the disease. However, according to the authors, it is too early to confirm a direct causal link between gene silencing, IGFBP-2 levels, and diabetes risk. The conclusions come from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort and involved measuring IGFBP-2 concentrations in plasma samples of a random subcohort of 2,500 individuals (there were 820 incident cases of type 2 diabetes up to the censoring date). The authors also constructed a nested 1:1 matched case-control sample for DNA methylation profiling of the *IGFBP-2* gene. Associations were then assessed via various modeling approaches after adjusting for a long list of factors that might affect any associations. They found that (after adjustment) higher circulating IGFBP-2 levels were linked to a lower BMI, waist circumference, and a range of biochemical measures. Higher levels of IGFBP-2 were also associated with lower type 2 diabetes risk, with the association holding for all five quintiles they defined in the analysis. An additional nonlinear modeling approach generally agreed with the initial analysis. Turning to the DNA methylation analysis, they found that a methylation score based on seven type 2 diabetes–related CpG sites in the *IGFBP-2* gene also correlated with diabetes risk. They go on to discuss mechanisms that might be involved and suggest that further animal and Mendelian randomization studies might now be appropriate. Author Annette Schürmann commented: "This paper nicely shows how translational research works. Findings from a broad screen performed in mice were picked up, mechanistically analyzed in the laboratory, and finally examined in a population-wide study."

Wittenbecher et al. Insulin-like growth factor binding protein 2 (IGFBP-2) and the risk of developing type 2 diabetes. Diabetes 2019;68:188–197

Brain Glucose Levels Reduced in Type 1 Diabetes Following Hyperglycemia

Individuals with type 1 diabetes experience a diminished rise in brain glucose levels following an acute episode of modest hyperglycemia, according to Hwang et al. (**p. 163**). As a result, the authors suggest that the brain might adapt to diabetes conditions by reducing the amount of glucose that can enter the brain and that this may be to protect it from excess glucose. Initially focusing on humans, the authors recruited 14 individuals with type 1 diabetes and 9 healthy control subjects to participate in 5 days of continuous glucose monitoring (with a Dexcom G4 device). This was followed by a 2-h hyperglycemic clamp procedure while undergoing magnetic resonance spectroscopy to measure glucose levels in the brain. In addition to this, they report experiments with rats in which groups with and without streptozotocin-induced diabetes underwent clamp procedures followed by nuclear magnetic resonance spectroscopy of various brain regions to measure glucose levels. They found that in humans, despite similar changes in plasma levels of glucose in the clamp procedure, individuals with type 1 diabetes had significantly smaller increases in brain glucose. They also found that the change in brain glucose levels positively correlated with a glucose lability index measurement (describing changes in glucose over time). Turning to the animal experiments, they report that, consistent with the human investigation, rats with induced diabetes also had lower brain glucose levels in various brain areas (cortex, hippocampus, and striatum) in comparison to controls. Discussing the outcomes, they suggest that the diminished brain glucose levels might represent some form of protective mechanism for the brain against the effects of increased glucose. They also highlight the correlation between glucose variability and brain glucose levels and suggest that more research is needed on the factors that contribute to the phenomenon.

Hwang et al. Glycemic variability and brain glucose levels in type 1 diabetes. Diabetes 2019;68:163–171

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