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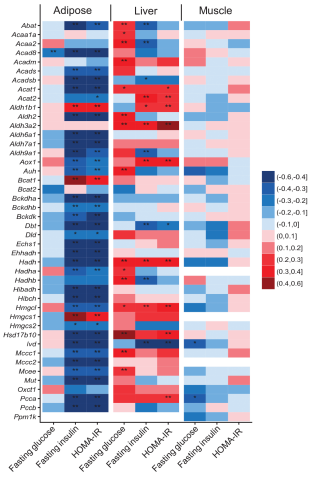
In This Issue of *Diabetes*

By Max Bingham, PhD

Possible Treatment Options for Insulin Resistance in Obesity via Branched-Chain Amino Acid Pathway

A disruption to branched-chain amino acid (BCAA) homeostasis likely plays a pivotal role in obesity-related insulin resistance and diabetes according to Zhou et al. (**p. 1730**). They demonstrate that defects in the BCAA catabolic pathway and the resulting abnormal accumulation of BCAA and branched chain α-keto acid (BCKA) metabolites likely play a causal role in the pathogenesis of obesity-associated insulin resistance. And, as a proof of concept, they provide evidence that it is possible to modify these pathways and to treat insulin resistance and diabetes, at least in mouse models of obesity and insulin resistance. Initially focusing on human genomic data sets from genome-wide association studies and gene expression analyses, they identify adipose tissue–specific BCAA-related gene modules that are associated with obesity-related insulin resistance. To then link this human data to the mouse models typically used for studying insulin resistance, they turned to a panel of genetically diverse mouse strains to look at BCAA catabolic genes in various tissues, largely confirming the observations from the human data. Moving to a mouse model of obesity and diabetes, they found that there was systemic suppression of BCAA catabolic genes and that this led to deficiency in the rate-limiting BCKA dehydrogenase. To then confirm the link to insulin resistance, the authors used a pharmacological intervention with 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid to restore BCAA catabolism and found that this markedly attenuated insulin resistance. They also found that manipulating diet to alter general and BCAA-specific amino acid intake levels largely recapitulated the effects of BCAA on insulin resistance. Finally, insulin sensitivity could also be restored in diet-induced obesity in mice with 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid, suggesting there might well be therapeutic options with the BCAA catabolic pathway. Author Haipeng Sun told *Diabetes*: "Our data offer a compelling mechanistic basis for the strong association observed between elevated plasma BCAA/BCKA and insulin resistance in the clinic, highlighting the therapeutic potential of reducing dietary protein intake or enhancing BCAA catabolism to prevent or treat insulin resistance."

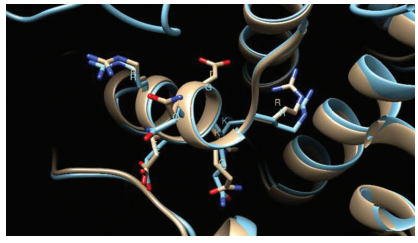


The BCAA catabolic pathway shows a strong correlation with insulin resistance in a mouse population. Correlation of individual BCAA catabolic genes in different tissues for fasting glucose, fasting insulin, and HOMA-IR in HMDP mice fed an HFD. Red indicates a positive correlation, whereas blue indicates a negative correlation.

Zhou et al. Targeting BCAA catabolism to treat obesity-associated insulin resistance. Diabetes 2019;68:1730–1746

Novel Autoantigen Improves Prediction of Type 1 Diabetes in At-Risk Individuals

A new variant of the autoantigen IA-2 has been identified by Acevedo-Calado et al. (**p. 1819**), which they report reacts with sera of individuals at risk for progressing to type 1 diabetes. Termed IA-2var, the autoantibody is reportedly associated with accelerated progression to type 1 diabetes especially in younger and older first-degree relatives of type 1 diabetes index case subjects, irrespective of whether they have single, multiple, or no other islet autoantibodies. Apart from having relevance in identifying individuals at high risk for type 1 diabetes that would otherwise be classified as low risk on the basis of the "traditional" autoantibodies for the condition, the authors suggest it could be used to identify individuals that might benefit from participation in prevention trials. The discovery comes from the TrialNet Pathway to Prevention Study and involved just under 1,700 individuals who were first-degree relatives of individuals with type 1 diabetes but who did not have diabetes themselves. Following screening for a series of islet autoantibodies, they were then followed for the next 8 years (on average) to identify individuals who developed type 1 diabetes. In addition to the usual autoantibody screening, they also included an assay for IA-2var. A total of 566 individuals progressed to diabetes in the follow-up period. The authors found that individuals with IA-2var had associated accelerated progression when they were also positive for the GAD65 and/or insulin autoantibodies but not IA-2. They also found that first-degree relatives of index case subjects carrying the IA-2var and one other autoantibody as well as the HLA-DRB1*04-DQB1*03:02 haplotype progressed very rapidly to type 1 diabetes. On that basis, they suggest that including the IA-2var autoantibody might allow better characterization of risk of progression and thus the identification of individuals who might benefit from inclusion in prevention trials.



Predicted three-dimensional structural model showing residues RQQD**KER for native IA-2 (gold) and SNP_2 residues RQQ**G**KER for IA-2var (blue).**

Acevedo-Calado et al. Autoantibodies directed toward a novel IA-2 variant protein enhance prediction of type 1 diabetes. Diabetes 2019;68:1819–1829

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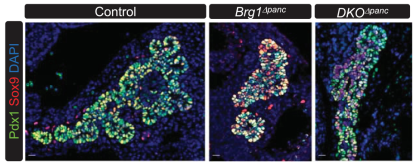
Early-Stage Cell Development in the Pancreas: Pdx1, Swi, Snf, and Chromatin

Spaeth et al. (**p. 1806**) have investigated a potential pathway and cellular complex that might dictate how early progenitor cells divide to become the various cell types that make up the pancreas. Crucially, they show how β-cells might form in the very early stages of embryonic development and how a complex of factors, collectively called Pdx1:Swi/Snf, are likely to control pancreas development, the eventual size of the pancreas, and also the fate of the insulin-producing β-cells. The upshot, they claim, is that targeting the complex and its interactions might present opportunities for therapies, particularly for type 2 diabetes. Using approaches that reveal the development of multipotent pancreatic progenitor cells in various mouse models, they show that pancreas size and islet β-cell function appear to be controlled by ATP-dependent Swi/Snf chromatin remodeling coregulatory complex. They explain that the complex physically associates with Pdx1 (pancreas and duodenum homeobox1), a diabetes-linked transcription factor. Additionally, they point out that it is a transcription factor that is essential to pancreatic growth and its functional development. Using deletion approaches with the mouse models, they found that early embryonic deletion of the Swi/Snf Brg1 ATPase subunit reduced pluripotent cell proliferation and reduced pancreas size. However, further genetic removal of the subunits for the enzyme did finally remove islet β-cell activity. The result was, according to the authors, glucose intolerance, hyperglycemia, and impaired insulin secretion. Further genetic analyses go some way to explain the observations, including the idea that β-cells might be "empty" in that they can exist but do not produce insulin. The bottom line, the authors explain, is that pancreas size and β-cells losing their ability to produce insulin remain the biggest challenges to solve in diabetes.



MPC proliferation is dependent on the Brg1 ATPase subunit of Swi/Snf. A representative immunostaining image of Sox9⁺ and Pdx1⁺ cells in control, *Brg1*$^{\Delta panc}$, and *DKO*$^{\Delta panc}$ pancreata at e12.5.

Spaeth et al. The Pdx1-bound Swi/Snf chromatin remodeling complex regulates pancreatic progenitor cell proliferation and mature islet β-cell function. Diabetes 2019;68:1806–1818

Hybrid Insulin Peptides Detected in Peripheral Circulation in New-Onset Type 1 Diabetes

Studies have established that hybrid insulin peptides (HIPs) can form in human and murine islets and that they are targeted by diabetes-triggering CD4 T cells. HIP-reactive CD4 T cells can also be detected in the islets and peripheral blood of NOD mice, suggesting their potential as disease biomarkers. Baker et al. (**p. 1830**) have now shown that HIP-reactive T cells can also be detected in the peripheral blood of patients with recent-onset type 1 diabetes. The authors tested responses to 16 distinct HIPs through enzyme-linked immune absorbent spot analyses on peripheral blood mononuclear cells obtained from 35 individuals with new-onset type 1 diabetes and 19 control subjects without diabetes. They report that, compared with controls, more of the subjects with type 1 diabetes responded to one or more of the HIPs in the panel, with the majority of the responders reacting to multiple HIPs. In contrast, just one control subject showed reactivity to multiple HIPs. Responses to 4 of the 16 HIPs reached significance in patients with type 1 diabetes, while none of the responses reached significance in the control group. In addition, they show how HIP-reactive T cells can react to HIP ligands even at low nanomolar concentrations and that they can persist for up to 1 year post–disease diagnosis. Authors Rocky L. Baker and Thomas Delong commented: "This is the first report that HIP-reactive T cells can be observed in the peripheral blood of human subjects and points to a variety of reactivities among patients with type 1 diabetes that go beyond those observed in the islets of donors with type 1 diabetes. We anticipate that additional HIP specificities will be revealed in the future, that HIP-reactive T cells may serve as biomarkers for disease, and that HIPs may serve as targets for antigen-specific tolerance induction strategies."

Baker et al. Hybrid insulin peptides are autoantigens in type 1 diabetes. Diabetes 2019;68:1830–1840

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