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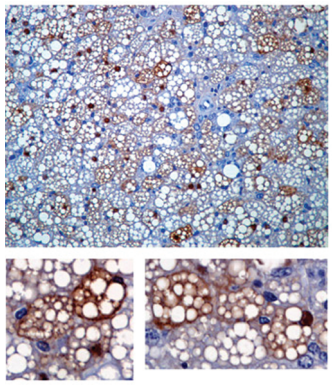
In This Issue of *Diabetes*

Edited by Helaine E. Resnick, PhD, MPH

Novel Tool for Studying the Pathophysiology of Obesity and Diabetes

Adeno-associated viral (AAV)–mediated engineering of adipose tissue may emerge as a valuable tool for the development of new therapies for both obesity and type 2 diabetes. Impaired activity or mass of brown adipose tissue (BAT) and white adipose tissue (WAT) are known contributors to obesity and type 2 diabetes in both animal models and humans. Although genetic engineering of adipose cells could shed light on the molecular mechanisms underlying obesity and diabetes, in vitro studies have encountered numerous technical challenges that have inhibited forward movement toward a better understanding of molecular mechanisms. Both cultured immortalized precursor cell lines and primary adipocytes may also differ in important ways from adipocytes in vivo, potentially limiting the application of in vitro findings. In the new work presented in this month's issue of *Diabetes*, Jimenez et al. (**p. 4012**) examined AAV vectors of serotypes 1, 2, 4, 5, 6, 7, 8, and 9 in order to determine whether these vectors could transduce murine WAT and BAT in vivo. The investigators found that AAV8 and AAV9 vectors mediated long-term, efficient transduction of WAT and BAT in adult lean and obese-diabetic mice. These results were observed both with local and systemic administration. Importantly, the findings of a recent study that reported proinflammatory cytokines in the liver following intravenous administration of double-stranded AAV vectors in mice were not consistent with observations in the new report, which demonstrated no inflammation of the liver or adipose tissue following intravenous administration of single-stranded AAV8 or AAV9 vectors. The investigators highlight the application of their findings by suggesting that AAV vectors could be used for genetic engineering of adipose tissue not only to study diabetes pathophysiology, but also for the development of novel therapies. — *Laura Gehl, PhD*



Immunostaining against green fluorescent protein (brown) in sections of intrascapular BAT.

Jimenez et al. In vivo adeno-associated viral–mediated genetic engineering of white and brown adipose tissue in adult mice. Diabetes 2013;62:4012–4022

ECL-GADA Assay May Improve Prediction of Type 1 Diabetes

Intriguing research presented in this issue of *Diabetes* (**p. 4174**) examines the sensitivity of a new electrochemiluminescence (ECL) assay for the detection of islet autoantibodies. Improved identification of islet autoantibodies, which can appear years before the onset of diabetes, could not only help predict type 1 diabetes, but would assist in population screening efforts, identification of environmental factors that increase type 1 diabetes risk, and risk stratification among those who test positive. The ECL-GAD antibody (GADA) assay that is highlighted in the new report is an extension of the previous work by Miao et al. that led to the development of an ECL-insulin autoantibody (IAA) assay with superior sensitivity and specificity than the standard micro-IAA radioassay. In the new study, Miao et al. used serum samples from four groups: children newly diagnosed with type 1 diabetes; prediabetic children who were followed to type 1 diabetes; nondiabetic children with confirmed islet autoantibodies to insulin, GAD65, IA2, and/or ZnT8; and healthy antibody-negative children who served as control subjects. Sensitivity of the ECL-GADA assay was similar to the GADA radioassay in children newly diagnosed with type 1 diabetes, prediabetic children, and children with multiple islet autoantibodies. However, less than one-quarter of nondiabetic children who were positive for GADA only by radioassay were also positive for ECL-GADA. Follow-up of these children indicated that those who were positive for GADA by radioassay and negative by the ECL assay remained ECL negative for years despite multiple positive follow-up tests by radioassay. Further, none of the GADA radioassay-positive/ECL-negative children developed a second islet autoantibody or diabetes. These results seem to indicate that the ECL-GADA assay can better identify individuals who are truly at higher risk of type 1 diabetes, a finding that is important considering that 30–60% of children in previous studies have been positive for only one autoantibody, mostly IAA or GADA. These individuals are at low risk of developing diabetes, suggesting that the new assay may yield fewer false positives if used for screening. These preliminary results indicate that the ECL-GADA assay is capable of differentiating high-risk islet autoantibodies from less disease–relevant antibodies and may help to improve the prediction of type 1 diabetes. — *Laura Gehl, PhD*

Miao et al. GAD65 autoantibodies detected by electrochemiluminescence assay identify high risk for type 1 diabetes. Diabetes 2013;62:4174–4178

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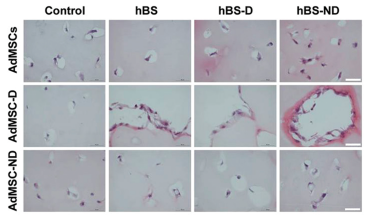
Key Role for Lactate in Counterregulatory Failure

In this issue of *Diabetes*, new work by Chan et al. (**p. 4239**) indicates that lactate contributes to increased γ-aminobutyric acid (GABA) levels in the ventromedial hypothalamus (VMH) of recurrently hypoglycemic (RH) and diabetic rats by enhancing GABA release. Clinically, hypoglycemia is the primary factor limiting the ability of patients with diabetes intensively treated with insulin to attain proper glycemic control. Improved understanding of the factors that contribute to hypoglycemia have the potential to enhance the safety of insulin use, thereby facilitating improved glycemic control for people who are unable to reach target on oral medications. Previous studies have shown that increased GABA, an inhibitory neurotransmitter in the VMH, contributes to the failure of counterregulatory responses to hypoglycemia. However, the mechanism underpinning this failure has not been fully established. In the current study, Chan et al. delivered L-lactate, or artificial extracellular fluid (aECF), into the VMH of RH and diabetic rats by microdialysis. L-lactate increased GABA levels in the VMH, thereby suppressing counterregulatory responses to hypoglycemia. When 4CIN, an inhibitor of lactate transport, or oxamate (OX), an inhibitor of lactate dehydrogenase, was injected into the VMH prior to inducing hypoglycemia, 4CIN or OX restored counterregulatory responses in both RH and diabetic rats by lowering VMH GABA levels. Further, blocking $GABA_A$ receptors with bicuculline, a $GABA_A$ receptor antagonist, also reversed counterregulatory responses, although unlike 4CIN or OX, bicuculline did not prevent the lactate-induced rise in GABA. These data suggest that lactate increases GABA levels in the VMH, thus contributing to counterregulatory failure in RH and diabetes. This mechanism may be a viable target for new therapies that aim to mitigate hypoglycemia in patients with intensively treated diabetes. — *Laura Gehl, PhD*

Chan et al. Lactate-induced release of GABA in the ventromedial hypothalamus contributes to counterregulatory failure in recurrent hypoglycemia and diabetes. Diabetes 2013;62:4239–4246

Report Suggests Unfavorable Impact of Diabetic Milieu on Stem Cell Performance

Although patients with type 2 diabetes who suffer from critical limb ischemia (CLI) may benefit from regenerative stem cell therapies, a recent trial in which two patients developed distal thrombosis raised questions about the safety of these new therapies. In this issue of *Diabetes*, new work by Acosta et al. (**p. 4266**) suggests that harvesting stem cells from, or implanting them into, a diabetic environment may affect the ability of the cells to perform vital functions like fibrin breakdown. The CLI therapy examined in the new report involved intra-arterial implantation of stem cells derived from adipose tissue. Acosta et al. conducted a number of experiments using serum samples from individuals with CLI (half of whom had diabetes) and healthy individuals as culture media for stem cells. The cells were sourced from CLI patients with and without diabetes as well as healthy control subjects. For cells from the diabetic source, expression of tissue plasminogen activator (tPA), which is critical for fibrinolysis, was lower, and levels of PAI-1, a tPA inhibitor, were elevated. Notably, when stem cells were embedded into fibrin clots, the fibrinolytic activity of cells from the nondiabetic source was visibly decreased in the presence of diabetic serum compared with nondiabetic or control sera. Furthermore, levels of D-dimer, indicative of fibrin breakdown, were similarly reduced in the diabetic medium whether the source was diabetic or not. These novel findings suggest that adequate fibrinolytic function may be better safeguarded with the addition of preclinical safety tests, such as D-dimer and/or tPA/PAI-1 ratio tests, before CLI patients with type 2 diabetes receive stem cell therapy. — *Wendy Chou, PhD*



Hematoxylin and eosin staining shows adipose-derived mesenchymal stromal cells (AdMSCs)–mediated lysis of the fibrin gel.

Acosta et al. Adipose mesenchymal stromal cells isolated from type 2 diabetic patients display reduced fibrinolytic activity. Diabetes 2013;62:4266–4269

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