OCTOBER 2014

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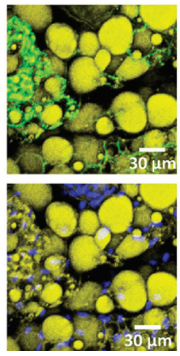
In This Issue of *Diabetes*

Edited by Helaine E. Resnick, PhD, MPH

Lactate Stimulates the Browning of White Adipose Cells

Brown adipose tissue (BAT) may have untapped therapeutic potential for treating metabolic disorders including type 2 diabetes and obesity because it not only dissipates energy through the expression of uncoupling protein 1 (*Ucp1*), but it also plays a role in diet and nonshivering thermogenesis. BAT can emerge from white fat in a process called "browning," but how this process occurs has remained elusive. In this issue of *Diabetes*, Carrière et al. (**p. 3253**) investigate the role of lactate in the browning process and show that this metabolic intermediate—once considered only a glycolytic waste product—may be a critical player in the browning of BAT. In the newly published work, the investigators took on the question of whether lactate contributes to browning via the expression of functional *Ucp1*. Their experiments demonstrated that lactate enhanced thermogenic *Ucp1* expression in murine and human adipose cells, with no parallel increase in expression of *Ucp2*. In vitro imaging suggested that lactate-induced browning resulted from new UCP1-positive cells as well as activation of preexisting low UCP1 cells. The results also showed that lactate-induced browning requires active peroxisome proliferator–activated receptor γ signaling. To extend these findings in vivo, mice were treated with daily intraperitoneal lactate injections for 11 days and the resulting impact on *Ucp1* was examined. The results showed that lactate alone did not change *Ucp1* expression in interscapular BAT (iBAT) fat pads. Treating mice with rosiglitazone also had no significant effect on *Ucp1* expression in iBAT. While coinjection of lactate and rosiglitazone still showed no enhancement of *Ucp1* in iBAT, the coinjection did result in a significant increase in *Ucp1* expression in subcutaneous white adipose cells compared with mice that only received rosiglitazone. Taken together, these results demonstrate that lactate stimulates the browning of white adipose cells in mice and humans via changes in *Ucp1* gene expression. — *Laura Gehl, PhD*

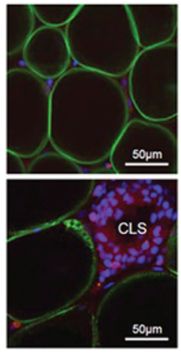


High magnification of inguinal section of control mice.

Carrière et al. Browning of white adipose cells by intermediate metabolites: an adaptive mechanism to alleviate redox pressure. Diabetes 2014;63:3253–3265

Macrophage HIF-2α Helps Maintain Homeostasis After Metabolic Change

Data in this issue of *Diabetes* suggest that a hypoxia-induced transcription factor may help alleviate proinflammatory responses that are observed in adipose tissue. Adipose tissue macrophages (ATMs) are thought to contribute to metabolic dysfunction including insulin resistance and type 2 diabetes, and they play an important role in regulating proinflammatory responses in this tissue. Both hypoxia-inducible factor (HIF)-1α and HIF-2α are transcription factors that mediate hypoxic responses like angiogenesis, glycolysis, adhesion, and infiltration. However, HIF-2α has been studied less than HIF-1α, particularly with regard to whether it functions differently from HIF-1α in adipose tissue. In a new series of experiments, Choe et al. (**p. 3359**) observed that HIF-2α mRNA was elevated in the adipose tissue of obese *db/db* mice compared with lean controls, and that overexpression of macrophage HIF-2α decreased nitric oxide production by increasing levels of arginase 1. Other results showed that *Hif-2α*$^{+/-}$ mice were susceptible to adipose tissue inflammation and insulin resistance in the setting of diet-induced obesity. Clodronate injections improved glucose tolerance in high-fat diet–fed *Hif-2α*$^{+/-}$ mice via the depletion of macrophages and brought glucose tolerance levels within the same range as those observed in high-fat diet–fed wild-type mice. Collectively, the data reported in this issue of *Diabetes* indicate HIF-2α plays a key role in helping ATMs maintain homeostasis in response to metabolic changes. These findings suggest increased HIF-2α activity may present a novel approach for treating obesity-related metabolic disorders. — *Laura Gehl, PhD*



HIF-2α is elevated in the ATMs from *db/db* mice. CLS, crown-like structure.

Choe et al. Macrophage HIF-2α ameliorates adipose tissue inflammation and insulin resistance in obesity. Diabetes 2014;63:3359–3371

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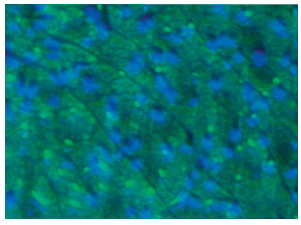
A New Role for Cyclin D1: Regulation of Gluconeogenesis via PGC1α

Intriguing data in this issue of *Diabetes* demonstrate a new role for cyclin D1 in glucose homeostasis via its regulation of peroxisome proliferator–activated receptor γ coactivator (PGC)-1α. Although maintenance of normal blood glucose during fasting or nutrient deprivation requires hepatic gluconeogenesis, when this process is poorly regulated—when suppression of gluconeogenesis does not occur—it can lead to hyperglycemia and type 2 diabetes. Not surprisingly, improved understanding of signaling pathways that control suppression of hepatic glucose output offers tremendous potential for developing new therapies that are linked to this aspect of glucose metabolism. To better understand suppression of gluconeogenic gene expression, Bhalla et al. (**p. 3266**) extended their previous work in this area by investigating the role of cyclin D1, a cell-cycle regulator, in this process. Cyclin D1 is expressed in the liver and is best known for activating cyclin-dependent kinase 4 (CDK4). The newly published data show that cyclin D1 expression was reduced in fasted mice. Refeeding not only induced expression of cyclin D1, it also reduced the expression of genes associated with gluconeogenesis and oxidative phosphorylation (OxPhos), including *Pgc1α*. In a separate series of experiments in which hyperglycemic mice were treated with a CDK4 inhibitor, refeeding resulted in higher expression of gluconeogenic and OxPhos gene expression, including *Pgc1α*, relative to mice that did not receive the inhibitor. In vivo experiments involved the use of the CDK4 inhibitor in PGC1α liver-specific knockout ($Pgc1\alpha^{LK0}$) mice. Although inhibition of CDK4 in wild-type mice blocked the inhibitory effects of refeeding on gluconeogenic and OxPhos gene expression, there was no significant increase in these genes in the $Pgc1\alpha^{LK0}$ mice. These results indicate a role for PGC1α as a mediator of D1 regulation. Although these findings shed new light on signaling pathways that are closely linked with hepatic glucose output, the authors urge caution about the therapeutic implications of these early findings because of cyclin D1's known function as a cell-cycle regulator. — *Laura Gehl, PhD*

Bhalla et al. Cyclin D1 represses gluconeogenesis via inhibition of the transcriptional coactivator PGC1α. Diabetes 2014;63:3266–3278

A Curcumin Derivative Targets JNK Signaling and Inhibits Cardiomyopathy

Work by Pan et al. (**p. 3497**) in this issue of *Diabetes* provides evidence that C66—a curcumin derivative—inhibits Jun NH_2-terminal kinase (JNK)-associated injury to the diabetic heart. In recent years, the role of inflammation in the pathogenesis of both diabetes and diabetic vascular complications has sparked interest in stress-activated, proinflammatory pathways as potential targets for pharmacologic development. The activity of JNKs, which regulate signaling in inflammatory cytokines and apoptosis, have been prime targets for this line of investigation. The newly published work shows that JNK signaling was inhibited in response to pretreatment with C66. The investigators tested the effects of C66 administration both in vitro (cultured H9c2 heart-derived stem cells and primary cultures of neonatal cardiac cells) and in vivo. The H9c2 cells were treated with C66 for 2 h and then exposed for 22 h to either high (HG) or low glucose (LG). Under HG conditions, C66 treatment significantly—and in a dose-dependent manner—inhibited mRNA expression of cytokines interleukin (IL)-12, IL-1β, and IL-6 down to or below levels observed under LG conditions. Levels of tumor necrosis factor (TNF)-α protein in H9c2 cells were also significantly reduced by C66 under HG, as were TNF-α and IL-6 levels in cardiac cells that were pretreated with C66/HG. Furthermore, HG-induced apoptosis in cardiac cells was also attenuated by treatment with C66, another observation supporting its protective effects. Examination of the hearts of type 1 diabetic mice treated with C66 over 2 months revealed a host of protective effects on cardiac function, ranging from a reduction in histological abnormalities, fibrosis, and cell apoptosis associated with diabetic cardiomyopathy, to a restoration of diastolic and systolic left ventricles. These findings warrant further study of C66 as a potential anti-inflammatory therapeutic agent for cardiomyopathy, and they advance a fundamental understanding of the JNK mechanism by suggesting that blocking this pathway mediates glucose-induced inflammation and apoptosis. — *Wendy Chou, PhD*



Heart tissues (5 μm section) were processed for p65 immunocytochemistry.

Pan et al. Inhibition of JNK phosphorylation by a novel curcumin analog prevents high glucose–induced inflammation and apoptosis in cardiomyocytes and the development of diabetic cardiomyopathy. Diabetes 2014;63:3497–3511

DOI: 10.2337/db14-ti10