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Highlights From the Latest in Diabetes Research

Of Mice and Men: New Data on Beige Adipocytes

In 2009–2010, 78 million U.S. adults aged ≥20 years were obese—a number representing 35.7% of the adult population. As the prevalence of obesity continues its alarming rise among both adults and children, the need for novel approaches to prevention and treatment is increasingly urgent. New research from the Spiegelman laboratory contributes to the growing body of literature concerning the potential therapeutic implications of "beige" adipocyte regulation. It is well established that white adipose tissue primarily functions in energy storage (triglycerides) and as an endocrine organ (adipokines), whereas brown adipose tissue generates heat and plays an important role in maintaining energy homeostasis. Mice that are genetically manipulated to have higher levels of brown fat also have more pronounced antiobesity and antidiabetic profiles. The current study shows that a third class of adipocytes (beige) is present within white adipose tissue depots, that beige adipocytes have a gene expression pattern that is distinct from both brown and white adipocytes, and that beige adipocytes are derived from a unique precursor population. In an initial series of experiments in mice, the researchers show that beige adipocytes have a low basal expression of UCP1 that is similar to white adipose tissue, but when stimulated, UCP1 levels increase as much as 150-fold, resulting in an absolute level of UCP1 similar to that observed in brown adipose tissue. Additional experiments showed that irisin, a hormone that is secreted by muscle and upregulated during exercise in a manner that results in the "browning" of white adipose tissue, selectively upregulated UCP1 genes in beige adipocyte precursors, suggesting that these precursor cells are sensitive to the browning effects of irisin. Finally, data from brown adipose tissue biopsies of two independent human cohorts showed that brown adipose tissue had gene expression signatures resembling beige cells in mice and that UCP1-positive cells had the same beige cell markers observed in mice. These results indicate that what has previously been thought of as brown fat in humans has characteristics that are more similar to murine beige fat. These data offer insights into how regulation of this new class of adipocytes might be harnessed for development of novel therapies to fight the obesity epidemic. — *Helaine E. Resnick, PhD, MPH*

■ Wu et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell 2012;150:366–376

Novel Findings on the Inter-relationships of VGF, Nkx6.1, and Glucose-Stimulated Insulin Secretion

Diabetes results from a number of metabolic abnormalities including decreased insulin action in muscle and fat, uncontrolled hepatic glucose output, and decreases in β-cell mass and function. Compensatory hyperinsulinemia keeps glucose in check until the unfavorable impact of diabetes on β-cells causes a relative decrease in insulin levels that results in frank diabetes. The key role that decreased β-cell mass and function play in diabetes onset makes these pathways appealing targets for development of therapeutic agents. A number of these products are currently on the market, including those that function through stimulating insulin release, slowing or preventing loss of β-cell mass, as well as agents that preserve β-cell function and survival. It is against this backdrop that Stephens et al. have published new data from an ongoing line of investigation into the role of the transcription factor Nkx6.1. Previous experiments from this laboratory showed that Nkx6.1 had two favorable effects on rat islets: increased β-cell replication and enhanced glucose-stimulated insulin secretion (GSIS). In the current series of experiments, the investigators demonstrate that Nkx6.1 upregulates the prohormone VGF and that it is the increase in VGF production that is responsible for the observed association between Nkx6.1 and improved GSIS. These experiments also showed that TLQP-21, a VGF peptide, potentiated GSIS in isolated islets of both rats and humans and that this peptide shares a number of properties of exendin-4, a GLP-1R agonist, such as improving GSIS and glycemic control, as well as reducing islet cell apoptosis. Further, administration of this peptide delayed diabetes onset in ZDF rats by reducing islet cell destruction. Of interest, TLQP-21 did not reduce gastric emptying or increase heart rate—two side effects of exendin-4 that can result in discontinuation of therapy in some patients. Taken together, these new data suggest that TLQP-21 may be a promising target for new therapies aimed at preservation of β-cell mass and function. — *H.E.R.*

■ Stephens et al. A VGF-derived peptide attenuates development of type 2 diabetes via enhancement of islet β-cell survival and function. Cell Metab 2012;16:33–43

Relative Benefits of Strength Training and Aerobic Physical Activity in Prevention of Type 2 Diabetes

Although engaging in regular physical activity (PA) is a cornerstone of preventive medicine, recommendations concerning the frequency, intensity, and duration of PA have evolved over time, largely in response to the growth in clinical research on the health benefits of exercise. Although it has been some time since the U.S. Surgeon General (SG) adopted a recommendation that adults engage in 150 min of moderate to vigorous PA each week, a number of issues, such as how (e.g., in what intervals) the 150 min should be allocated, how much moderate or vigorous PA should be done in the recommended time frame, and what types of PA confer health benefits, have resulted in additions to the SG's original recommendations. These modifications were aimed at promoting adoption of PA recommendations among all Americans by helping people tailor PA to their individual needs and personal preferences. Currently, the SG's PA recommendations specify that aerobic activity (150 min of moderate aerobic PA, 75 min of vigorous aerobic PA each week, or an equivalent mix) should be supplemented by muscle strength training on 2 or more days each week. Ideally, these strength training activities should work all major muscle groups. It is against the backdrop of these updated PA recommendations that new data on the relative benefits of aerobic PA and strength training in the primary prevention of diabetes should be considered. The investigators followed a cohort of >32,000 male health professionals for ~18 years. Self-reported data on weekly time spent doing aerobic PA and strength training were collected at baseline and biennially during follow-up. For both aerobic PA and strength training, results showed a dose-response relationship between time spent in either of these types of PA and decreased risk of diabetes. The association between strength training and decreased diabetes risk was observed independently of time spent in aerobic activity, and men who engaged in both types of PA experienced greater benefit than those who engaged in only one. The investigators suggest that these are the first data to demonstrate the independent benefits of strength training on prevention of diabetes, and they support the idea that diabetes risk can be substantially reduced among individuals who prefer strength training over aerobic PA. — H.E.R.

■ Grøntved et al. A prospective study of weight training and risk of type 2 diabetes mellitus in men. Arch Intern Med. 6 August 2012 [Epub ahead of print]

Regulating the Temporality of Food Intake: A Potential Nonpharmacological Intervention for Obesity Prevention?

Recent attention has focused on the potential role of circadian dysfunction in the pathogenesis of obesity and type 2 diabetes. A growing body of literature in both humans and rodents suggests that disrupted sleep patterns result in increased body weight and abnormalities of glucose regulation and that these effects may be mediated, at least in part, by the inter-relationships of the circadian clock with metabolism, energy homeostasis, and the timing of meals. Intriguing data from Hatori et al. provide new insight into the potential importance of meal timing on metabolic abnormalities, independent of total energy intake. The new data derive from a series of experiments in which mice were fed either normal chow or a high-fat diet (HFD) and in which feeding occurred either ad libitum or in a time-restricted manner during normal feeding times. Animals were followed for 18 weeks during which all groups consumed the same amount of calories regardless of the feeding paradigm. Relative to ad libitum fed mice on the HFD, which developed obesity, hyperinsulinemia, and hepatic steatosis, time-restricted mice on the same HFD did not experience these complications. The investigators then examined metabolic regulators that might help explain these observations and showed that mice on the ad libitum HFD had perturbed oscillations in pCREB and pS6. Time-restricted mice on the same diet had diurnal food intake cycles that restored normal peaks in these key regulators, and they also had increased hepatic AMP relative to the ad libitum HFD animals. Together, these data strongly suggest that regulation of food intake rhythms may play a critical role in obesity and its related metabolic disorders and that these mechanisms operate independently of total energy intake. These results also suggest that behavioral interventions focusing on this aspect of energy balance may be a promising avenue for further investigation. Indeed, these data may be particularly relevant because many humans now have a "24-h lifestyle" that is characterized by frequent snacking, shorter sleep duration, and a less structured approach to mealtimes—all features that the current research suggests may work against the potential metabolic benefits of time-restricted feeding. — H.E.R.

■ Hatori et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metab 2012;15:848–860

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