The Secret Life of Fat Suggests New Therapeutic Targets

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Not so many years ago, most considered fat a passive recipient of our indulgence. But since the discovery of leptin in 1994,1 it has become ever clearer that fat is more than a storage site for excess calories. Rather, fat plays an active, communicative role in metabolism that research is beginning to uncover.

Two recent studies not only represent our rapidly changing grasp of the biology of fat but also suggest potential treatments for one of the world’s most intractable chronic health conditions: obesity. A paper in Nature2 in January 2012 from the laboratory of Bruce Spiegelman, PhD, of the Dana-Farber Cancer Institute in Boston, MA, reported the discovery of a new hormone released by muscle that converts white fat deposits into thermogenic brown fat. Whereas white fat acts as a repository for excess, mitochondria-rich brown fat cells burn ordinary fat as energy to produce heat. Once thought to only exist in rodents and infants, several groups have confirmed brown fat in humans. It is found in small patches along the spine, in the upper back, on the sides of the neck, and between the collarbone and shoulder.

A few weeks after Spiegelman’s Nature paper was published, a publication3 in the Journal of Clinical Investigation from the laboratory of Shelia Collins, PhD, of the Sanford-Burnham Medical Research Institute in Orlando, FL, revealed the heart plays a role in the regulation of fat burning. Collins, first author Marica Bordicchia, and colleagues reported that cardiac natriuretic peptides increased browning of white fat, elevating uncoupling protein 1 (UCP1)–dependent energy expenditure.

C. Ronald Kahn, MD, chief academic officer at the Joslin Diabetes Center in Boston, MA, says the recent discoveries are likely just the opening act in our growing knowledge about fat metabolism. “Right now we’re looking at the first things that have been discovered. They’re already very interesting,” Kahn said. “There will be more factors discovered for sure, because, once you realize there is this metabolic flexibility to this tissue, then it begins to challenge you to think, ‘I wonder what will change the metabolic potential of this tissue?’”

During the last 10 years, Spiegelman’s laboratory and others demonstrated that the transcription factor that regulates mitochondrial biogenesis, peroxisome proliferator activated receptor-γ coactivator 1-α (PGC1-α), mediated most of the effects of endurance exercise on muscle.4 “It is induced by exercise, and, in turn, when it’s elevated in muscle, it gives muscle many of the benefits of exercise: mitochondrial biogenesis, fiber-type switching, increased angiogenesis, resistance to atrophy and dystrophy,” Spiegelman said. “So it wasn’t that big a stretch to ask, ‘Does PGC1-α in muscle secrete something that may affect health and function of other tissues?’”

In the new study, Spiegelman, first author Pontus Boström, and colleagues found that PGC1-α increases expression of the membrane protein FNDC5. FNDC5 is cleaved and secreted as a previously unidentified hormone that browns white fat, turning it into energy-burning multilocular cells, rich in mitochondria and high in expression of UCP1. The researchers called the newly discovered hormone irisin (pronounced eye-risin), after Iris, the Greek messenger goddess. Certain white fat cells respond sharply to irisin, which is 100% conserved from mice to humans. Cells treated with uncleaved FNDC5 had dose-dependent increases of UCP1 mRNA from 7- to 500-fold. Cells treated with bone morphogenic protein 7 (BMP7), known to induce browning of white fat, gave rise to only a 2-fold increase in UCP1 expression.

Obese, insulin-resistant mice treated with an adenoviral vector expressing FNDC5 had slightly reduced body weight after 10 days compared with controls. In addition, glucose tolerance improved significantly in FNDC5 mice fed a high-fat diet. Although circulating irisin never rose above a 3-fold increase, similar to the irisin upick generated by exercise, UCP1 expression rose 10- to 20-fold. Subcutaneous white fat browned and increased its energy use. Finally, when...
mice were treated with an antibody against FNDC5, the browning effects of exercise declined dramatically. “It’s plausible that irisin is a contributor, even a significant contributor, to the metabolic effects of exercise,” Spiegelman said. “Irisin alone may lessen obesity and help with glucose control. It could be a therapy for metabolic disease and other disorders that normally improve with exercise, especially in the population that cannot exercise: those with muscular dystrophy, amyotrophic lateral sclerosis, or severe arthritis.”

The discovery of something like irisin in muscle was not unexpected, but rather awaited, said Vihang Narkar, PhD, who studies transcriptional regulation of skeletal muscle function at the University of Texas Health Science Center at Houston. “It has been proposed for a while that muscle actually acts as an endocrine organ,” Narkar says. “But the discovery of a muscle-specific factor has been illusive to this point. So it’s not a surprise that a factor is released by muscle, and it definitely will not be the last one or the only one. This opens a whole new area of investigation, which is the endocrine effects of skeletal muscle.”

In February 2012, Collins’ team provided insight into adipose metabolism from a different direction. Their paper showed an important role for the heart in the regulation of adipose tissue via cardiac natriuretic peptides (NPs), both atrial natriuretic peptide (ANP) and ventricular or B-type natriuretic peptide (BNP).

There were previously only hints of a relationship between these cardiac peptides and fat. For instance, when ANP is added to the growth media of cultured human adipocytes, the cells release stored fat the same way they would in the presence of adrenaline. Another clue came from NPs released as a result of exercise-induced increases in cardiac output. Those NPs regulate fatty acids in the skeletal and cardiac muscle under aerobic conditions. Also suggestive: Obese people with metabolic syndrome have lower levels of circulating NPs, and repeated studies have shown the higher the body mass index, the lower the plasma NPs. Finally, the paper points out, natriuretic peptides serve as an indicator of severity in cachexia in chronic heart failure.

The findings from Collins’ laboratory now elucidate a clear pathway for the effects of ANP and BNP in inducing human and mouse white adipocytes to acquire features of energy-expending brown adipocytes. “If we can understand more about this process and how to manipulate it, and how to target it, there might be multiple benefits,” Collins says, including in the treatment of hypertension, metabolic disease, and obesity.

Using both in vivo and in vitro approaches, Collins’ team showed that NPs increase expression of UCP1 and PGC1-α in both white and brown fat depots, turning on all the machinery of brown adipocyte thermogenesis. Increasing expression of UCP1 enhances respiration, allowing mitochondria in fat cells to release energy as heat rather than in the creation of ATP from ADP. Increased PGC1-α contributes to the net increase in mitochondrial capacity to meet the demands caused by rising UCP levels.

The classic pathway to drive energy-costly thermogenesis in brown adipocytes and browning of white fat cells is via the sympathetic nervous system during exposure to cold. In that pathway, activation of β-adrenergic receptors increases levels of cAMP, activating cAMP-dependent protein kinase (PKA), which phosphorylates targets in adipocytes. A 2004 study by Collins’ group (Spiegelman was a coauthor) showed this pathway is dependent on p38α mitogen-activated protein kinase (p38α MAPK) to transcribe Ucp1 and Pgc1-α.

The new study shows that NPs use a similar pathway, starting with the natriuretic protein receptor A, which activates cGMP, and cGMP-dependent protein kinase (PKG). PKG phosphorylates the same adipocyte targets as the adrenergic system’s PKA and, the study shows, is also dependent on p38α MAPK.

This insight showing similar pathways to thermogenesis and browning of white fat cells suggests potential therapeutic targets, perhaps free of the pitfalls of other compounds that increase energy dissipation in brown adipose tissue, said Antonio Vidal-Puig, MD, PhD, who studies the molecular mechanism of energy balance in the Institute of Metabolic Science, University of Cambridge Metabolic Research Laboratories, United Kingdom.

“The JCI paper is opening doors, opening doors to the concept that the heart can activate thermogenesis in brown adipose tissue, and this is completely new,” said Vidal-Puig, who coauthored a commentary on the paper by Bordicchia et al in the same issue of the Journal of Clinical Investigation. “This is going to attract quite a lot of attention,” he said.

“I think it’s very remarkable that you can have a parallel system of activating brown fat that is not dependent on adrenergic tone,” Vidal-Puig said. “Most obesity treatments that were very successful at causing weight loss all finally failed for the same reason,” he said: their indiscriminate interactions with adrenergic receptors throughout the cardiovascular system. Ephedrine and sibutramine, which acted on the adrenergic system, successfully increased brown fat activation, but they also increased the risk of heart attack, stroke, hypertension, and elevated heart rate.

Vidal-Puig said the long-term impact of NPs on body weight awaits determination. “Nor is it clear how much the system contributes to normal energy balance,” he said. “I think that this is not its main function.” The paper in the Journal of Clinical Investigation also did not report NPs on mice that were already obese.

Finally, it will be critical to determine whether NPs affect other organs in the same manner that their ill-fated obesity-drug predecessors have. “However, the ability of NPs to modulate the effects of endogenous sympathetic nervous system activation in [brown adipocyte tissue] makes them an exciting candidate for future intervention,” Vidal-Puig writes.

References
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