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. 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 Bostrm, 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 expression. FNDC5 proteolytically cleaves.

Irisin, a hormone named for the Greek messenger goddess Iris, was recently discovered in the Spiegelman laboratory.

- It is secreted by muscle during exercise when membrane protein FNDC5 proteolytically cleaves.
- It is formed from the fibronectin III domain of FNDC5.
- Its 112-amino acid structure is 100% conserved between human and mouse, without even conservative substitutions.
- It stimulates the expression of UCP1 and browning in subcutaneous adipose tissue.

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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, amytrophic 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.5 Another clue came from NPs re-
leased as a result of exercise-induced increases in cardiac
output. Those NPs regulate fatty acids in the skeletal and
cardiac muscle under aerobic conditions.6 Also suggestive:
Obese people with metabolic syndrome have lower levels of
circulating NPs,7 and repeated studies have shown the higher
the body mass index, the lower the plasma NPs.8,9 Finally, the
paper points out, natriuretic peptides serve as an indicator of
severity in cachexia in chronic heart failure.10

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 mito-
chondria 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’ group11 (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 acti-
vates cGMP, and cGMP-dependent protein kinase (PKG).
PKG phosphorylates the same adipocyte targets as the adren-
ergic 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 Lab-
oratories, 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.12
“Is this 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 cardio-
vascular 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.

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