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CLINICAL IMPLICATIONS OF BASIC RESEARCH

# A Muscular Twist on the Fate of Fat

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Article

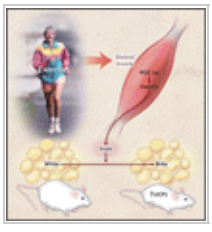
Hippocrates observed that “walking is man's best medicine” and thus underscored the benefits of physical activity to health. More than two millennia later, the benefits of physical activity in lowering the risk of death from any cause and improving longevity have been well documented.[1] Scientists are also beginning to understand the benefits of exercise on a molecular level and to consider skeletal muscle as an endocrine organ, capable of communicating with other tissues through myokines, which are released into the circulation during physical activity. In a recent study, Boström and colleagues[2] identified a new myokine, irisin, which is released into the circulation during exercise and triggers the transformation of white fat cells into brown-in-white, or brite, cells — white fat cells with a phenotype similar to that of brown fat cells.

Well over a decade ago, a transcriptional coactivator (a molecule involved in the regulation of gene expression) was identified by Lin and colleagues,[3] who in a series of studies found that this transcriptional coactivator, peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), plays a critical role in the maintenance of glucose, lipid, and energy homeostasis. They also found that PGC-1α is involved in the pathologic processes associated with obesity-related disorders, such as diabetes, cardiovascular disease, and neurodegeneration. Moreover, mice engineered to constitutively express PGC-1α in their muscles are resistant to age-related obesity and diabetes and have an increased lifespan,[4] a finding that suggests that PGC-1α, in addition to its effect within the skeletal muscle, may regulate the metabolism of other tissues — notably, white adipose tissue.

The aim of the study by Boström and colleagues was to identify the language of the crosstalk between PGC-1α–expressing skeletal muscle and white adipose tissue. When comparing the genes that are expressed in the muscle of wild-type mice with those expressed in the muscle of transgenic mice (mice engineered to express high levels of PGC-1α), they observed greater expression of several genes encoding certain secreted protein products, including a protein called fibronectin type III domain containing 5 (FNDC5). The researchers observed that FNDC5 is proteolytically cleaved (dubbing its cleavage product “irisin,” after the Greek messenger goddess, Iris) and that its expression in skeletal muscle increases with exercise in both mice and humans. In humans, plasma levels of irisin after 10 weeks of regular exercise were twice as high as baseline levels.

The researchers then injected obese mice with adenoviral particles engineered to express FNDC5; these mice had plasma irisin levels that were three to four times as high as the levels in mice injected with adenoviral particles containing a control gene. The white adipose tissue of the mice with higher irisin levels also had a high level of expression of uncoupling protein 1 (UCP1), which is characteristic of brown adipose tissue. UCP1 funnels the energy generated from respiration into heat production. This change was accompanied by an increase in total body energy expenditure, modest weight loss, and modest improvements in glucose intolerance (Figure 1).

**FIGURE 1**



Cross-Talk between Muscle and Fat.

The view that adult humans possess brown fat is now well accepted. Moreover, recent evidence shows that the metabolism of brown fat is increased when adult humans are exposed to cold.[5] Therefore, the finding by Boström and colleagues that exercise (through the influence of irisin) has the capacity to turn on a phenotype similar to that of brown fat is likely to be of clinical significance for human metabolism. Further supporting this conclusion is the fact that the mouse and human irisin proteins are identical, although it remains to be seen whether irisin has the same effect on white adipose tissue in humans that it has on the white adipose tissue of mice.

Boström and colleagues have provided a mechanistic explanation for one aspect of the benefit of exercise: its protection against metabolic disease. However, their study has a broader significance in that it provides a conceptual basis for understanding how muscles communicate with other tissues. Exercise stimulates the release of multiple myokines, which offers protection against a network of diseases, including cardiovascular diseases, type 2 diabetes, cancer, dementia, and osteoporosis. It will be exciting to see how these protective effects are achieved at the molecular level.

Given the antiobesity and antidiabetic effects of brown-fat formation in mice, it is possible that patients who are unable to

exercise because of severe musculoskeletal or cardiovascular conditions could benefit directly from the discovery of irisin. But because exercise orchestrates the interplay of many secreted and nonsecreted proteins and has direct and indirect benefits on organs such as the brain and on the cardiovascular system, a single “exercise pill” will probably never replace the full effect of a good workout. And so, with a nod to Hippocrates, I suggest that you keep moving and activate all of your myokines.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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