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METABOLIC DISEASE

Exercise hormone fights metabolic disease

The transcriptional co-activator PPARγ co-activator 1α (PGC1α) has a central role in the regulation of cellular energy metabolism. Its expression is induced by exercise in muscle, where it mediates various beneficial effects. Now, writing in *Nature*, Boström and colleagues demonstrate that increased muscle PGC1α expression also positively affects adipose tissue — it stimulates the production and secretion of the novel hormone irisin from the muscle, which activates thermogenesis in fat, resulting in weight loss and improved glucose homeostasis in obese mice.

Exercise improves metabolic status in obesity and type 2 diabetes, but the underlying molecular mechanisms are poorly understood. Given that muscle PGC1α expression is elevated upon exercise, and transgenic mice with mildly elevated muscle PGC1α (MCK-PGC1α mice) are resistant to age-related obesity and insulin resistance, Boström and colleagues set out to investigate a possible role of muscle PGC1α in the beneficial metabolic effects of exercise.

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First, they analysed the adipose tissue of MCK-PGC1α mice and discovered that mRNA levels of thermogenic genes characteristic of brown fat, including the brown adipocyte marker uncoupling protein 1 (UCP1), were significantly increased in subcutaneous white adipose tissue (WAT) — an effect termed 'browning'. This thermogenic gene programme was similarly induced when control mice were exposed to wheel running or swimming in warm water.

Next, they treated cultured primary subcutaneous adipocytes with media conditioned by myocytes expressing PGC1α, and found mRNA levels of several brown-fat-specific genes to be increased in the adipocytes. This suggested that the browning they observed in mice may be mediated by a molecule secreted from muscle under the regulation of PGC1α.

To search for such a molecule, they analysed muscle from MCK-PGC1α mice using gene expression arrays and an algorithm that predicts protein secretion, and identified five candidate proteins. Applying these proteins directly to primary white adipocytes during differentiation revealed that one of them — fibronectin type III domain-containing protein 5 (FNDC5) — potently upregulated the expression of UCP1 and other brown fat genes, whereas it downregulated the expression of genes characteristic of WAT development. Importantly, *FNDC5* mRNA expression was increased in muscle from mice and humans, following exercise.

Further *in vitro* studies revealed that FNDC5 undergoes proteolytic cleavage and glycosylation to produce a highly conserved 112-amino-acid secreted polypeptide, which they named irisin. Irisin was detected in mouse and human plasma, and its levels were increased upon exercise.

Finally, they assessed the biological and therapeutic effects of irisin. Mildly increasing irisin levels in mice by injecting adenoviral vectors expressing FNDC5 induced WAT browning; this resulted in increased energy expenditure, reduced body weight and improved glucose tolerance in obese, insulin-resistant mice. When anti-FNDC5 antibodies were injected into mice prior to swimming, this prevented browning, indicating a requirement for irisin in this exercise-associated effect.

Together, these findings may have implications for the future treatment of metabolic disease. Indeed, Ember Therapeutics, co-founded by the lead author of this study, is currently generating variants of irisin in preparation for clinical trials.

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ORIGINAL RESEARCH PAPER Boström, P. *et al.* A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* **481**, 463–468 (2012)