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Irisin, a novel myokine: potential role in obesity and diabetes

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Abstract

Obesity is a worldwide health problem that results in a significant increased risk of morbidity and mortality. While we know that obesity is the consequence of a chronic imbalance between energy intake and energy expenditure, how energy expenditure is regulated in humans is not clearly understood. Recent publications suggest that specific depots of white adipose tissue can be converted to thermogenically active beige adipose tissue and that the myokine, irisin may be a key regulator of this conversion. ■ Heart Metab; 2013;61:39–40

Keywords: Brown adipose tissue; energy expenditure; irisin; myokine.

According to the World Health Organization, worldwide obesity has doubled since 1980, with more than 1.4 billion adults now considered to be overweight or obese. In the USA more than 60% of the adult population is now considered to be overweight or obese [1]. Obesity is associated with a number of comorbidities including type 2 diabetes, cerebrovascular and coronary heart disease, sleep apnea, pulmonary dysfunction, knee osteoarthritis, nonalcoholic steatosis, and certain types of cancer.

In simple mathematical terms, obesity is caused by chronic excess energy intake relative to energy expenditure (EE). In practice, however, the equation is not that simple. We know that there is considerable individual variation in the susceptibility to weight gain, and the ability to lose weight. This individual variability is highlighted by studies demonstrating significant heterogeneity in response to sustained caloric excess or deficit. In both acute [2] and chronic [3] over-feeding studies, for example, variability in weight gain was evident despite tight compliance with supervised mealtimes, indicating that differences in EE may be driving this variability [4]. Although the mechanisms underpinning this are uncertain, it is likely that a wide variation exists in physiological controls governing energy balance, helping to maintain an individual's body weight within a given range [5].

While fat free mass can explain approximately 80% of the variance in 24-hour EE [6], there is still considerable variability in energy requirements between individuals. The 20% variation in EE has a potentially tremendous impact on the prevalence and severity of obesity in the general population. One potential biological source of variable EE is adipose (fat) tissue, in particular brown adipose tissue (BAT), which clearly contributes to EE in some animals including mice and rats. Although BAT is present in newborn humans, its existence and function in adult humans has been debated [7]. Recent reports using positron emission tomography suggest the presence of active BAT in some, but not all, adults [8]. Furthermore, there appears to be a correlation between the presence of active BAT and increased EE in response to stimuli such as cold exposure and

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Abbreviations

BAT: brown adipose tissue; **EE:** energy expenditure; **PGC-1α:** proliferator-activated receptor-gamma coactivator-1α

the consumption of capsaicin [9, 10]. The regulation of BAT in humans is poorly understood; however, a recently discovered peptide, irisin, may play a role in the regulation of EE and metabolism. Irisin is a proliferator-activated receptor-gamma coactivator-1α (PGC-1α)-dependent myokine shown to induce "browning" of white adipose tissue, resulting in increased thermogenesis in mice [11]. Muscle-specific overexpression of PGC-1α in mice induced the expression of the *Fndc5* gene in muscle, which encodes a type 1 membrane protein that is proteolytically cleaved to produce a secreted plasma hormone named irisin [11]. Adenoviral expression of *Fndc5* in mice increased *Ucp1* and *Cidea* gene expression in subcutaneous white fat, resulting in increased EE and resistance to diet-induced obesity and diabetes. Exercise increases plasma irisin levels in both mice and humans. It is unclear why exercise would stimulate irisin synthesis when conservation of calories to fuel exercise would seem paramount. One hypothesis suggests that irisin is released from shivering muscle to induce thermogenesis and prevent hypothermia [11]. Furthermore, an additional contribution of fat to EE could be attributed to the adipokines leptin and adiponectin [12]. Irisin may play a role alongside leptin and adiponectin in the maintenance of lean and fat mass, and may well predict the efficacy of sustainable weight loss.

In addition to irisin's proposed role in energy balance it may also be involved in insulin resistance and type 2 diabetes [13]. Irisin levels have been reported to increase with exercise and to be lower in patients with type 2 diabetes [14]. A role for irisin in insulin action is supported by the report that two single nucleotide polymorphisms in the *FNDC5* gene have been associated with insulin sensitivity, as measured *in vivo* [15]. Furthermore, irisin levels have been reported to correlate inversely with intrahepatic fat content in obese adults [16]. At this point there are many unanswered questions, but it is important to determine whether irisin plays a role in mediating the beneficial effects of exercise on metabolism and EE.

It is clear that obesity results in an increased risk of diabetes and metabolic diseases and that exercise increases insulin sensitivity and metabolic health. However, the exact mechanisms and physiological pathways responsible are not clearly understood. The recently discovered myokine, irisin, may be an important link between exercise and its benefits on body weight, diabetes and metabolic health. ■

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