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Editorial

Irisin: A true, circulating hormone

1. New Kids on the Block

The existence and the role of irisin, as well as the quality of commercial enzyme-linked immunosorbent assay (ELISA) kits used to detect circulating irisin, have been recently matters of debate [1]. Irisin (named after the ancient Goddess, Iris, who served as a messenger among the Gods in Greek mythology) is a myokine, initially shown to be secreted by skeletal muscle in mice and humans [2]. Irisin has been proposed to drive the "browning" of the white adipose tissue [2], defined by the increased presence of thermogenic brown adipocytes in white adipose tissue [3]. By increasing energy expenditure, irisin is expected to be associated with some of the well-recognized benefits of exercise, including improved metabolism, cardiovascular health and cognition [4], and may represent a key player in the complex interactions between the skeletal muscle and other tissues implicated in energy homeostasis and metabolism [5].

Irisin is produced by the proteolytic cleavage of the extracellular domain of a transmembrane protein called fibronectin type III domain containing (FNDC)5, which is encoded by the *Fndc5* gene [1]. *Fndc5* gene has a non-canonical start codon, being ATA, instead of the more typical start codon, being ATG. Some authors have supported that ATA start codon in human *Fndc5* gene is a null mutation, which cannot lead to a protein production; they also supported that the downstream translation of *Fndc5* gene cannot provide the polypeptide described as irisin [6,7]. Furthermore, skepticism has been raised on the quality (lack of specificity) of commercial ELISA kits currently used for the measurement of circulating irisin in most published articles [6,8], as it has been recently reviewed [1].

A novel publication, by the group that first identified irisin [2], has recently reported a strong piece of evidence favoring irisin as a true circulating protein [9]. Jedrychowski et al. [9] used a methodologically refined procedure to measure circulating irisin with quantitative mass spectrometry. Two synthesized peptides (parts of irisin) were enriched with heavy stable isotopes (six ^{13}C atoms) and used as internal standards for mass spectrometry. These peptides were chosen because they are unique to the irisin sequence and not encoded in any other protein in the annotated human genome. By using liquid chromatography–tandem mass spectrometry, the authors validated that the synthetic "heavy" irisin peptides can be used for the identification and quantification of irisin. Next, irisin was quantified in a group of young and healthy volunteers subjected to aerobic training, as well as a group of sedentary controls, showing that circulating irisin levels were higher in the former than the latter (approximately 4.3 vs. 3.6 ng/ml, respectively). Plasma samples had previously been treated: 1) with a resin to remove the abundant albumin and immunoglobulins, so as to facilitate the analysis of less abundant proteins, including irisin, and 2) with the Protein Deglycosylation Mix, so as to completely deglycosylate. After electrophoresis, the anti-irisin antibody detected a band running at approximately

Abbreviations: AGA, appropriate-for-gestational-age; AHEI, alternate healthy eating index; ALT, alanine transaminase; AST, aspartate transaminase; AMPK, 5' adenosine monophosphate-activated protein kinase; aMED, alternate Mediterranean diet score; BMI, body mass index; CK, creatine kinase; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular-signal-regulated kinase; FNDC, fibronectin type III domain containing; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HMW, high molecular weight; HOMA-IR, homeostasis model of assessment insulin resistance; IL, interleukin; IUGR, intrauterine-growth-restricted; LETO, Long Evans Tokushima Otsuka; LGA, large-for-gestational-age; NAFLD, nonalcoholic fatty liver disease; MVPA, moderate and vigorous-intensity physical activity; OLETF, Otsuka Long-Evans Tokushima Fatty; PGC, peroxisome proliferator-activated receptor gamma coactivator; PNPLA, patatin-like phospholipase domain-containing protein; PPAR, peroxisome proliferator-activated receptor; SGA, small-for-gestational-age; SNP, single nucleotide polymorphism; STAT, signal transducer and activator of transcription; T2DM, type 2 diabetes mellitus; TNF, tumor necrosis factor; VO2, oxygen uptake.

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12 kDa, the predicted size of the irisin polypeptide [9]. Therefore, the authors provided strong evidence that irisin is a true peptide that circulates at a level higher than insulin and lower than leptin and adiponectin [9]. Last, but not least, the investigators used the two synthetic peptides to investigate FNDC5 mRNA translation start site. One peptide was part of the protein encoded downstream from the ATA codon, but upstream of the first ATG codon, whereas the other peptide was downstream from both. Since both native peptides were present in circulation in similar quantities, the authors confirmed that irisin is mainly translated downstream from its non-canonical start codon, ATA, which is not a pseudogene, and it is not a downstream product of the more typical ATG start codon [9].

Although Jedrychowski et al. seem to have developed a state-of-the-art method for the quantification of human irisin in plasma (which does not rely on antibodies), they acknowledge that a part of irisin may have been lost during the sample preparation (removal of albumin and immunoglobulins, deglycosylation etc.), which may range empirically between 10% and 30%. Furthermore, the method is costly and demanding, largely relying on the availability and capabilities [9]. However, although it cannot be used for large-scale studies, it could be used as benchmark for testing existing assays or developing new, more specific ones.

For the history, Lee et al. had first determined the identity of FNDC5-immunoreactive bands detectable in human serum by mass spectrometry [10]. Their mass spectrometry analysis identified a unique peptide, mapped to the known sequence of irisin, within the 32 kDa and 24 kDa bands, possibly referring to glycosylated and deglycosylated, respectively, irisin dimers [10].

2. Articles on Irisin Published in "Metabolism"

"Metabolism" has published many articles on FNDC5 and/or irisin following its identification in 2012 [2], which are summarized in Table 1.

2.1. *In Vitro Studies*

Moon et al. evaluated the effect of irisin treatment on hippocampal neurogenesis in mouse H19-7 hippocampal neuronal cells [11], as well as on cell proliferation and malignant potential in mice and human cancer cell lines [12]. They showed that, although physiologic concentrations of irisin did not affect H19-7 hippocampal neuronal cell proliferation, pharmacologic doses of irisin increased cell proliferation by 70%–80%, which may be achieved via the signal transducer and activator of transcription (STAT)3 pathway [11]. This study opens a new window for future studies on physiologic and pharmacologic effect of irisn in mental disorders. On the other hand, irisin treatment had no effect on cell proliferation, adhesion and colony number of mice and human cancer cell lines [12].

2.2. *Animal Studies*

Roberts et al. [13] showed higher muscle expression of *FNDC5* and peroxisome proliferator-activated receptor gamma coactivator *(PGC)1α* (a key transcription factor regulating *Fndc5* gene) mRNA in obese and diabetic prone Otsuka Long-Evans Tokushima Fatty (OLETF) than Long Evans Tokushima Otsuka (LETO) rats, and a positive association between *FNDC5* mRNA and body fat mass. However, circulating irisin was similar in both groups. This seeming controversy may imply a separation between *FNDC5* mRNA expression and circulating irisin, which may be further affected by its clearance and/or other metabolic conditions.

Fain et al. [14] showed that irisin increased after 16–20 weeks of exercise training in pigs predisposed to hypercholesterolemia, but not normal ones; however, *FNDC5* mRNA and protein levels in skeletal muscle, epicardial or subcutaneous fat were not changed after chronic exercise in either a familial hypercholesterolemic strain or normal pigs.

Samy et al. [15] showed higher circulating irisin in sedentary hyperthyroid and hypothyroid rats than euthyroid controls. Furthermore, irisin was positively associated with creatinine kinase (CK), and increased after acute boots of exercise. The findings of this study imply a possible cross-talk between thyroid hormones and irisin, which both target molecular mechanism of energy expenditure. Furthermore, the positive association with CK may imply that irisin may, to an extent, be produced by the cytolysis of myocytes.

2.3. *Clinical Studies*

Huh et al. [16] published one of the first articles on irisin, early after its identification. In their extensive and comprehensive study, *FNDC5* mRNA was expressed highly in skeletal muscle, and muscle areas of other organs. They showed that irisin was positively correlated with biceps circumference, fat-free mass, and body mass index (BMI) and that muscle mass was the main predictor of circulating irisin in young and healthy individuals. Moreover, they showed that irisin increased after acute, but not chronic, exercise, a finding later replicated by most relevant studies. Finally, in another intrventional arm of the study, they showed that briatric surgery-induced weight loss resulted in irisin decrease.

Tsuchiya et al. [17] showed that acute resistance training increased circulating irisin more than endurance or combined resistance/endurance training, which showed minimal changes, in healthy men. It seems that the kind of exercise may play a role on circulating irisin, and that the differentiation between acute exercise effect (which seems to increase irisin) and chronic exercise effect (which does not seem to change irisin) is generalized and may need reconsideration.

Huh et al. [18] also showed that acute boots of vibration exercise increased circulating irisin, whereas chronic vibration exercise did not change irisin. In this regard, acute vibration exercise seems to have an effect on circulating irisin similar to resistance training, as shown by Tsuchiya et al. [17] above.

Park et al. [19] evaluated the association between circulating irisin and dietary factors (macronutrients, energy intake and dietary scores). However, their findings were rather negative, since they reported that irisin was not associated with any of the studied dietary factors.

Swick et al. [20] showed that irisin was not generally correlated with 24 h energy expenditure; however, irisin was correlated with 24 h energy expenditure in a subgroup of

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