

Irisin and Metabolic Disorders

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Received 2015 September 17; Revised 2015 September 23; Accepted 2015 September 26.

Keywords: Irisin, Metabolic Disorders, Myokines

1. Introduction

Skeletal muscle, as an endocrine organ, secretes several cytokines, known as myokines, which have a significant role in the coordination of several organs and tissues, as well as human homeostasis (1, 2). Irisin (112 amino acid) is a newly identified hormone that is released from skeletal muscle following exercise. This protein is transcribed from the fibronectin type III domain-containing protein 5 (FNDC5) gene, and is produced by proteolytic cleavage that releases FNDC5 (3). In addition to skeletal muscle, FNDC5 mRNA and irisin peptide has been found in human adipose tissue (4), cerebrospinal fluid (5) and breast milk (6). Irisin is secreted in response to peroxisome proliferator-activated receptor-gamma coactivator (PGC-1 α) activation via exercise (3). PGC-1 α , as a transcriptional coactivator, is involved in several biological processes associated with energy metabolism (7). PGC-1 α has an important role in the regulation of uncoupling protein 1 (UCP-1) at the transcriptional level (7), mitochondrial biogenesis and thermogenesis (8, 9). In vitro and in vivo studies have shown that irisin induces UCP-1 expression in adipose tissue and activates thermogenic function, thereby, enhancing energy expenditure. Irisin has an important role in the browning of certain white adipose tissue (WAT) (3). It is noted that the thermogenic effect of irisin in humans remains disputable. Some studies have indicated that irisin has no effect on the browning of human preadipocytes (10), so it appears that more studies are required.

Researchers have indicated that irisin is not only a myokine, but also a novel adipokine with a significant autocrine and endocrine function. They found that FNDC5/irisin has a special pattern of secretion, depending on the anatomical location of the adipose tissue (11). Some studies have reported that FNDC5/irisin has a secretion profile like other adipokines such as leptin (12). Also, irisin has a negative correlation with adiponectin. FNDC5

injection reduced the adiponectin level and it seems that irisin may have a direct effect on the adipocyte differentiation (13). OKIn addition, an inverse association between irisin and omentin has been reported (14).

In addition, it seems that irisin may be involved in insulin resistance and type 2 diabetes (T2D). It has been reported that irisin, which is decreased in T2D, is conversely associated with recently diagnosed T2D (15, 16). Two single nucleotide polymorphisms in the FNDC5 gene are associated with insulin sensitivity (17). On the other hand, some studies did not find any association between irisin and glucose homeostasis (18, 19). Additionally, the correlation of BMI and irisin is debatable. Some studies reported a positive correlation (20, 21), null (19) or even a negative correlation (4). BMI and fat mass can be modulated by exercising. Taken together, the effect of exercise on FNDC5/irisin levels should be considered, even though different studies have reported conflicting results that are dependent on many variables such as type, intensity and duration of exercise, acute or chronic phase of disease and subject status. After exercise, circulated and skeletal tissue irisin were raised in some studies, reduced in others and remained unchanged in still others; more studies are required to reveal these differences (22, 23). It is noted that dihydromyricetin (DHM), a natural flavonoid, can increase irisin levels in rats and humans. DHM, as a potent exercise mimetic, may benefit patients with metabolic disease (24).

A cohort study of non-diabetic adult subjects indicated that an increased irisin level is associated with insulin resistance, vascular atherosclerosis and carotid intima-media thickness (an indicator of vascular atherosclerosis) in humans. This study suggested that increased irisin levels may be due to enhanced release by adipose/muscle tissue in reaction to worsening insulin sensitivity or a compensatory mechanism against irisin resistance (25). Also, irisin is associated with increased risk of metabolic syn-

drome (MetS), cardiometabolic variables (systolic and diastolic blood pressure, fasting glucose, triglycerides and homeostasis model assessment for insulin resistance), and cardiovascular disease (CVD) in humans (20). The irisin plasma level is reported to be lower in lactating woman with gestational diabetes mellitus than in non-lactating controls or healthy lactating women (6), however, some studies have indicated a higher level of irisin in pregnant women with gestational diabetes compared to non-diabetic pregnant controls (5, 26), and a lower level in non-obese pregnant women after adjusting for BMI, lipids and glucose (5). Irisin may also be a potential therapeutic target in non-alcoholic fatty liver disease. The increased intrahepatic triglyceride deposit is an important factor in fatty liver pathogenesis. It seems that the plasma irisin level associates negatively with intrahepatic triglyceride content (27). Overexpression of FNDC5 enhances the expression of peroxisome proliferator-activated receptors (PPARs) mRNA in WAT. Also, pharmacological inhibition of PPAR α halts fat browning. This suggests that PPAR may have a possible role in mediating the effects of FNDC5 (28). Taking into account the association of PPAR α with fibroblast growth factor 21 (FGF-21), irisin may regulate intrahepatic triglyceride content through FGF-21. Also, reduced irisin level is associated with increased ALT and AST, so irisin probably has a protective function against hepatic steatosis (27).

Irisin decreases in chronic renal failure, and its lower level has an independent association with lower HDL levels (29). The protective role of HDL in the cardiovascular system is well known, so it is reasonable to consider a role for irisin in CVD, however, further studies are required.

Very recently, in vivo and in vitro results have indicated that irisin is important in cardiac function. Irisin inhibited H9C2 cell proliferation and improved its growth via the PI3K AKT pathway. These pathways, the P38MAPK and STAT3 pathway, were activated in the myocardium following injection of r-irisin (expressed and purified from *Pichia pastoris* cultures) in mouse models. Irisin plays a role in intracellular Ca²⁺ signaling, and mitochondrial thermogenesis in cardiomyoblasts (30). The role of FNDC5/irisin in development of the nervous system has been reported in several studies (31, 32). It seems that FNDC5/irisin may regulate cognitive functions, probably by expression of brain-derived neurotrophic factor (BDNF) in the brain (33). These results can uphold the hypothesis of an advantageous or protective role of exercise in brain function in neuropsychiatric and neurodegenerative disorders (Alzheimer's and Parkinson's diseases) (23, 34, 35). It has been indicated that irisin may be a novel biomarker for polycystic ovary syndrome (PCOS). Irisin levels significantly increased in PCOS patients compared with control

subjects (36).

2. Conclusions

Irisin is a novel myokine, but several questions must be answered. The main gaps of knowledge to be filled include the study of the translation of human FNDC5/irisin, recognition of irisin receptors, identification of molecular pathways, understanding the precise role of irisin in metabolic disorders and finding the range of circulating irisin levels in healthy and unhealthy subjects.

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