Avicenna J Med Biochem. 2016 June; 4(1):e33230. doi: 10.17795/ajmb-33230.

Published online 2016 January 23. **Editorial**

Irisin and Metabolic Disorders

Maryam Esfahani,[1] Mostafa Baranchi,[2] and Mohammad Taghi Goodarzi[3,*]

[1]Department of Clinical Biochemistry, Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, IR Iran
[2]Department of Physical Education and Sports Sciences, Tarbiat Modares University, Tehran, IR Iran
[3]Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadan, IR Iran

[*]*Corresponding author*: Mohammad Taghi Goodarzi, Hamadan University of Medical Sciences, Hamadan, IR Iran. Tel: +98-8138380462, Fax: +98-8138380208, E-mail: mt.goodarzi@umsha.ac.ir

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-1α) activation via exercise (3). PGC-1α, as a transcriptional coactivator, is involved in several biological processes associated with energy metabolism (7). PGC-1α 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 PPARα 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 PPARα 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 Ca^{2+} 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 (BNDF) 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.

References

1. Iizuka K, Machida T, Hirafuji M. Skeletal muscle is an endocrine organ. *J Pharmacol Sci.* 2014;**125**(2):125–31. [PubMed: 24859778].
2. Pedersen L, Hojman P. Muscle-to-organ cross talk mediated by myokines. *Adipocyte.* 2012;**1**(3):164–7. doi: 10.4161/adip.20344. [PubMed: 23700527].
3. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature.* 2012;**481**(7382):463–8. doi: 10.1038/nature10777. [PubMed: 22237023].
4. Moreno-Navarrete JM, Ortega F, Serrano M, Guerra E, Pardo G, Tinahones F, et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. *J Clin Endocrinol Metab.* 2013;**98**(4):E769–78. doi: 10.1210/jc.2012-2749. [PubMed: 23436919].
5. Piya MK, Harte AL, Sivakumar K, Tripathi G, Voyias PD, James S, et al. The identification of irisin in human cerebrospinal fluid: influence of adiposity, metabolic markers, and gestational diabetes. *Am J Physiol Endocrinol Metab.* 2014;**306**(5):E512–8. doi: 10.1152/ajpendo.00308.2013. [PubMed: 24398403].
6. Aydin S, Kuloglu T, Aydin S. Copeptin, adropin and irisin concentrations in breast milk and plasma of healthy women and those with gestational diabetes mellitus. *Peptides.* 2013;**47**:66–70. doi: 10.1016/j.peptides.2013.07.001. [PubMed: 23850897].
7. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell.* 1998;**92**(6):829–39. [PubMed: 9529258].
8. Uldry M, Yang W, St-Pierre J, Lin J, Seale P, Spiegelman BM. Complementary action of the PGC-1 coactivators in mitochondrial biogenesis and brown fat differentiation. *Cell Metab.* 2006;**3**(5):333–41. doi: 10.1016/j.cmet.2006.04.002. [PubMed: 16679291].
9. Villena JA, Carmona MC, Rodriguez de la Concepcion M, Rossmeisl M, Vinas O, Mampel T, et al. Mitochondrial biogenesis in brown adipose tissue is associated with differential expression of transcription regulatory factors. *Cell Mol Life Sci.* 2002;**59**(11):1934–44. [PubMed: 12530524].
10. Raschke S, Elsen M, Gassenhuber H, Sommerfeld M, Schwahn U, Brockmann B, et al. Evidence against a beneficial effect of irisin in humans. *PLoS One.* 2013;**8**(9):e73680. doi: 10.1371/journal.pone.0073680. [PubMed: 24040023].
11. Roca-Rivada A, Castelao C, Senin LL, Landrove MO, Baltar J, Belen Crujeiras A, et al. FNDC5/irisin is not only a myokine but also an adipokine. *PLoS One.* 2013;**8**(4):e60563. doi: 10.1371/journal.pone.0060563. [PubMed: 23593248].
12. Novelle MG, Contreras C, Romero-Pico A, Lopez M, Dieguez C. Irisin, two years later. *Int J Endocrinol.* 2013;**2013**:746281. doi: 10.1155/2013/746281. [PubMed: 24298283].

13. Arias-Loste MT, Ranchal I, Romero-Gomez M, Crespo J. Irisin, a link among fatty liver disease, physical inactivity and insulin resistance. *Int J Mol Sci.* 2014;**15**(12):23163–78. doi: 10.3390/ijms151223163. [PubMed: 25514415].
14. Panagiotou G, Mu L, Na B, Mukamal KJ, Mantzoros CS. Circulating irisin, omentin-1, and lipoprotein subparticles in adults at higher cardiovascular risk. *Metabolism.* 2014;**63**(10):1265–71. doi: 10.1016/j.metabol.2014.06.001. [PubMed: 25060690].
15. Choi YK, Kim MK, Bae KH, Seo HA, Jeong JY, Lee WK, et al. Serum irisin levels in new-onset type 2 diabetes. *Diabetes Res Clin Pract.* 2013;**100**(1):96–101. doi: 10.1016/j.diabres.2013.01.007. [PubMed: 23369227].
16. Hojlund K, Bostrom P. Irisin in obesity and type 2 diabetes. *J Diabetes Complications.* 2013;**27**(4):303–4. doi: 10.1016/j.jdiacomp.2013.04.002. [PubMed: 23659776].
17. Staiger H, Bohm A, Scheler M, Berti L, Machann J, Schick F, et al. Common genetic variation in the human FNDC5 locus, encoding the novel muscle-derived 'browning' factor irisin, determines insulin sensitivity. *PLoS One.* 2013;**8**(4):e61903. doi: 10.1371/journal.pone.0061903. [PubMed: 23637927].
18. Pekkala S, Wiklund PK, Hulmi JJ, Ahtiainen JP, Horttanainen M, Pollanen E, et al. Are skeletal muscle FNDC5 gene expression and irisin release regulated by exercise and related to health?. *J Physiol.* 2013;**591**(Pt 21):5393–400. doi: 10.1113/jphysiol.2013.263707. [PubMed: 24000180].
19. Timmons JA, Baar K, Davidsen PK, Atherton PJ. Is irisin a human exercise gene?. *Nature.* 2012;**488**(7413):E9–10. doi: 10.1038/nature11364. [PubMed: 22932392].
20. Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE, et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. *J Clin Endocrinol Metab.* 2013;**98**(12):4899–907. doi: 10.1210/jc.2013-2373. [PubMed: 24057291].
21. Stengel A, Hofmann T, Goebel-Stengel M, Elbelt U, Kobelt P, Klapp BF. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity–correlation with body mass index. *Peptides.* 2013;**39**:125–30. doi: 10.1016/j.peptides.2012.11.014. [PubMed: 23219488].
22. Aydin S. Three new players in energy regulation: preptin, adropin and irisin. *Peptides.* 2014;**56**:94–110. doi: 10.1016/j.peptides.2014.03.021. [PubMed: 24721335].
23. Chen N, Li Q, Liu J, Jia S. Irisin, an exercise-induced myokine as a metabolic regulator: an updated narrative review. *Diabetes Metab Res Rev.* 2015. doi: 10.1002/dmrr.2660. [PubMed: 25952527].
24. Zhou Q, Chen K, Liu P, Gao Y, Zou D, Deng H, et al. Dihydromyricetin stimulates irisin secretion partially via the PGC-1alpha pathway. *Mol Cell Endocrinol.* 2015;**412**:349–57. doi: 10.1016/j.mce.2015.05.036. [PubMed: 26054747].
25. Sesti G, Andreozzi F, Fiorentino TV, Mannino GC, Sciacqua A, Marini MA, et al. High circulating irisin levels are associated with insulin resistance and vascular atherosclerosis in a cohort of nondiabetic adult subjects. *Acta Diabetol.* 2014;**51**(5):705–13. doi: 10.1007/s00592-014-0576-0. [PubMed: 24619655].
26. Ebert T, Stepan H, Schrey S, Kralisch S, Hindricks J, Hopf L, et al. Serum levels of irisin in gestational diabetes mellitus during pregnancy and after delivery. *Cytokine.* 2014;**65**(2):153–8. doi: 10.1016/j.cyto.2013.11.009. [PubMed: 24355429].
27. Zhang HJ, Zhang XF, Ma ZM, Pan LL, Chen Z, Han HW, et al. Irisin is inversely associated with intrahepatic triglyceride contents in obese adults. *J Hepatol.* 2013;**59**(3):557–62. doi: 10.1016/j.jhep.2013.04.030. [PubMed: 23665283].
28. Hondares E, Rosell M, Diaz-Delfin J, Olmos Y, Monsalve M, Iglesias R, et al. Peroxisome proliferator-activated receptor alpha (PPARalpha) induces PPARgamma coactivator 1alpha (PGC-1alpha) gene expression and contributes to thermogenic activation of brown fat: involvement of PRDM16. *J Biol Chem.* 2011;**286**(50):43112–22. doi: 10.1074/jbc.M111.252775. [PubMed: 22033933].
29. Wen MS, Wang CY, Lin SL, Hung KC. Decrease in irisin in patients with chronic kidney disease. *PLoS One.* 2013;**8**(5):e64025. doi: 10.1371/journal.pone.0064025. [PubMed: 23667695].
30. Xie C, Zhang Y, Tran TD, Wang H, Li S, George EV, et al. Irisin Controls Growth, Intracellular Ca2+ Signals, and Mitochondrial Thermogenesis in Cardiomyoblasts. *PLoS One.* 2015;**10**(8):e0136816. doi: 10.1371/journal.pone.0136816. [PubMed: 26305684].
31. Hashemi MS, Ghaedi K, Salamian A, Karbalaie K, Emadi-Baygi M, Tanhaei S, et al. Fndc5 knockdown significantly decreased neural differentiation rate of mouse embryonic stem cells. *Neuroscience.* 2013;**231**:296–304. doi: 10.1016/j.neuroscience.2012.11.041. [PubMed: 23219938].
32. Moon HS, Dincer F, Mantzoros CS. Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines. *Metabolism.* 2013;**62**(8):1131–6. doi: 10.1016/j.metabol.2013.04.007. [PubMed: 23664146].
33. Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, et al. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. *Cell Metab.* 2013;**18**(5):649–59. doi: 10.1016/j.cmet.2013.09.008. [PubMed: 24120943].
34. Walker JM, Klakotskaia D, Ajit D, Weisman GA, Wood WG, Sun GY, et al. Beneficial effects of dietary EGCG and voluntary exercise on behavior in an Alzheimer's disease mouse model. *J Alzheimers Dis.* 2015;**44**(2):561–72. doi: 10.3233/JAD-140981. [PubMed: 25318545].
35. Erickson KI, Weinstein AM, Lopez OL. Physical activity, brain plasticity, and Alzheimer's disease. *Arch Med Res.* 2012;**43**(8):615–21. doi: 10.1016/j.arcmed.2012.09.008. [PubMed: 23085449].
36. Chang CL, Huang SY, Soong YK, Cheng PJ, Wang CJ, Liang IT. Circulating irisin and glucose-dependent insulinotropic peptide are associated with the development of polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2014;**99**(12):E2539–48. doi: 10.1210/jc.2014-1180. [PubMed: 25029417].