Review

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Can irisin be a linker between physical activity and brain function?

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Abstract: Irisin was initially discovered as a novel hormone-like myokine released from skeletal muscle during exercise to improve obesity and glucose dysfunction by stimulating the browning of white adipose tissue. Emerging evidence have indicated that irisin also affects brain function. FNDC5 mRNA and FNDC5/irisin immunoreactivity are present in various regions of the brain. Central irisin is involved in the regulation of neural differentiation and proliferation, neurobehavior, energy expenditure and cardiac function. Elevation of peripheral irisin level stimulates hippocampal genes related to neuroprotection, learning and memory. In this brief review, we summarize the current understanding on neuronal functions of irisin. In addition, we discuss the pros and cons for this molecule as a potential messenger mediating the crosstalk between skeletal muscle and central nervous system during exercise.

Keywords: brain function; exercise; FNDC5; irisin; myokine.

Introduction

The beneficial effects of physical activity for brain health and function have been recognized for centuries. Regular physical activity reduces a number of mental disorders such as depression and anxiety, as well as attenuates the onset and progression of Alzheimer's disease (AD) and Parkinson's disease (PD) (1). Recently, a large-scale 5-year prospective study in human subjects has demonstrated that regular physical activity could represent an important and potent protective factor for cognitive decline and dementia in the elders (2). Animal studies also demonstrate that exercise and/or behavioral enrichment significantly improves brain function measured by neuronal survival and resistance to brain insult (3, 4), brain vascularization (5, 6), neurogenesis (7), learning (7, 8), as well as maintenance of cognitive function during aging (9, 10).

Increased levels of neurotrophins in the central nervous system have been proposed to mediate the beneficial effects of regular physical activity. Among these neurotrophins, brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF-2), epidermal growth factor (EGF) and never growth factor (NGF) are well characterized to increase survival, proliferation and maturation of specific neurons in the brain (11). Emerging evidences also suggest a peripheral mechanism. Peripheral tissues such as adipose tissue and skeletal muscle may respond to exercise by producing leptin (12) and irisin (13) that bolster brain function.

Irisin, whose name derives from the Greek goddess Iris (messenger of the gods), is a novel hormone-like myokine released from skeletal muscle during exercise. This 112 amino acid peptide is cleaved from fibronectin type III domain containing protein 5 (FNDC5) (14). FNDC5/irisin has been found to be expressed robustly not only in skeletal muscle (14) but also in various regions of brain tissue (15–17). Since its discovery in 2012, this molecule has gained huge interest as a potential mediator of the health promoting effects of physical exercise. Exercise increases *Fndc5* gene expression in skeletal muscle, leading to subsequent increment in circulating irisin (14, 18). Similarly, endurance exercise increases expression of FNDC5 in the hippocampus (13). Overexpression of *Fndc5* in the liver results in significant elevation of circulating irisin. The change in blood irisin is associated with a marked increment in the expression of *Bdnf* and other neuroprotective genes in the hippocampus (13). All these findings suggest

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that irisin may serve as a critical molecule linking regular exercise with health and diseases of the brain. In this brief review, we summarize current understanding on the neuronal function of irisin. We will also discuss the pros and cons for this molecule as a potential messenger mediating the crosstalk between skeletal muscle and central nervous system during exercise.

Irisin in brain function

Emerging evidence has indicated that irisin may function as a neurotrophic factor to promote survival, maintenance and function of neuronal cells.

Effects of irisin on neural differentiation

The function of FNDC5 on neural differentiation was first discovered by a research team from Iran. Also named *PeP* transcript because it was independently discovered in a search for peroxisomal proteins, FNDC5 was initially demonstrated to be significantly increased after retinoic acid induction during the neural differentiation of mouse embryonic stem cells in neural precursor cells and neurospheres (19). This finding indicates that FNDC5 might be involved in the early regulation of neurogenesis. Knockdown of *Fndc5* in mouse embryonic stem cells significantly reduces expression of both neural progenitors and mature neuronal markers, which results in the reduction of both neuronal and astrocyte maturation (20). On the other hand, overexpression of *Fndc5* significantly increases neural differentiation precursor markers and mature neuron markers. All these data suggest that FNDC5 may facilitate neural differentiation (21). Further studies (22) indicate that FNDC5 stimulates neural differentiation via the extracellular-signal-regulated kinase 1/2(ERK1/2) signaling pathway.

Unlike its precursor FNDC5, irisin is less convincingly demonstrated to directly regulate neurogenesis. At physiologic concentrations from 5 to 10 nM, irisin demonstrates no effect on neuronal cell proliferation in cultured H19-7 cells, a mouse hippocampal cell line. Only pharmacological doses of irisin (50–100 nM) increase cell proliferation by 70%–80%. This alteration is mediated by the signal transducer and activator of transcription 3 (STAT3) signaling pathway (23). Further, neither physiological doses nor pharmacological concentrations of irisin affect neurite outgrowth and synaptogenesis in cultured H19-7 cells. In contrast, a recent study by Wrann et al. (13) shows that hepatic overexpression of *Fndc5* induces expression of *Bdnf* and other neuroprotective genes in the hippocampus. This effect is presumably mediated by irisin because its circulating level is significantly elevated. Further investigation should aim to characterize the direct regulation of neural differentiation and proliferation by irisin.

Neurobehavioral effects of irisin

The finding (13) that peripheral overexpression of *Fndc5* induces increment in BDNF expression in hippocampus hints that irisin may function to improve learning and memory by the BDNF pathway. *Bdnf*, a notable neurotrophin, promotes many aspects of brain development including neuronal cell survival, differentiation, migration, dendritic arborization, synaptogenesis and plasticity (24). BNDF is also essential for hippocampal function in learning and memory (25). Further, levels of cFos, Arc, and Zif268 in hippocampus and forebrain, which are important indicators for the activity state of neurons, increase significantly in mice overexpressing *Fndc5* (13). Together with the findings that endurance exercise elevates levels of circulating irisin, these results suggest the potential neurotrophic function of irisin. Irisin may thus be a critical molecule linking the beneficial effects of regular physical activity with the neurobehavioral improvement. This concept is further supported by our recent studies. Administration of irisin by third intracerebroventricular (ICV) injection causes an abrupt and transient increase in locomotor activity, including total travel distance, ambulatory counts and time (26). Interestingly, peripheral administration of irisin demonstrates no effect on locomotor activity (26).

However, it is worthy to note that direct application of irisin to cultured hippocampal neurons demonstrates negligible effect on the expression of *Bdnf* gene (13). Whether irisin regulates the hippocampal function via an indirect mechanism remains to be investigated.

Cardiac function of central irisin

Endurance exercise increases cardiac function. Our studies provide evidence supporting that irisin may contribute to the beneficial effect of exercise on cardiac function. Central administration of irisin significantly increases both systolic and diastolic blood pressure. Further, heart rate and cardiac output dose-dependently increase immediately following injection of 0.625, 1.25 and 2.5 μg irisin into the 3rd ventricle (27). These cardiotropic effects of central irisin may occur through activation of paraventricular nucleus

(PVN) neurons in the hypothalamus. Vasopressin but not norepinephrine may be responsible for pressor effects of central irisin. Conversely, other studies have found that irisin evokes bradycardia by increasing cardiac vagal tone of nucleus ambiguus (28). Microinjection of irisin in 50 nl of either 10^{-11}, 10^{-10}, 10^{-9} or 10^{-8} mol/l into the nucleus ambiguous significantly reduces the heart rate in conscious rats. In cultured nucleus ambiguus neurons, irisin at the doses from 10^{-10} mol/l to 10^{-8} mol/l activates these neurons by evoking an increase in cytosolic Ca^{2+} concentration and neuronal depolarization. The differential effects of irisin on cardiac function may be related to the difference in dose, targeting nuclei and animal conditions such as anesthetic or conscious.

Metabolic effects of central irisin

Irisin has been proposed to be a key player in improvements of obesity and glucose homeostasis induced with exercise (29). Mildly increased levels of irisin in circulation cause an increase in energy expenditure in mice with no change in food intake (14). The increase of total energy consumption induced by irisin may pertain to the stimulation of uncoupling protein 1 and the browning of white adipose cells (14). Our previous studies also suggest a central mechanism for the metabolic effects of irisin. Third ventricle administration of irisin significantly increases oxygen consumption, carbon dioxide and heat production (26), suggesting an increment in energy expenditure. This alteration is associated with an activation of the paraventricular nuclei in the hypothalamus, one of the major sympathetic outflows innervating adipose tissue. Together with muscle shivering and browning of fat cells, the rise in locomotion and heat production provides a broader and robust defense against hypothermia. Irisin could thus be a molecule connecting skeletal muscle with brain and adipose tissue to form a thermogenesis network.

Irisin as a messenger between exercise and brain functions: current controversies

We have highlighted evidence indicating that irisin may contribute to the regulation of brain function. We then discuss the following controversial questions regarding whether irisin may serve as a messenger linking the regular physical activity with brain function.

Is irisin synthesized and released from FNDC5 in the central nervous system?

Before the protein product of FNDC5 was named 'irisin' (14), the *Fndc5* gene was initially discovered and named '*PeP*' (15) and '*Frcp2*' (16) independently during the genome search for fibronectin type III domains and peroxisomal proteins. Using the whole-mount *in situ* hybridization, expression of *Frcp2* was demonstrated in the fore- and midbrain during mouse embryonic development. The expression of *Frcp2* in adult mouse brain was further confirmed by Northern hybridization (16). Consistently, studies by Ferrer-Martinez et al. also showed that PeP is strongly expressed in adult mouse and rat brain, whereas its level is low in embryonic and neonatal brain (15). In a recent study by Wrann et al. (13), *Fndc5* mRNA was detected in cortical neurons and hippocampus.

Recent studies also demonstrate the presence of FNDC5/irisin protein in various brain regions including cerebellum, hypothalamus and spinal cord. Using immunohistochemistry with an antiserum against irisin peptide fragment (42-112) (Phoenix Pharmaceuticals, Inc., Burlingame, CA), irisin-immunoreactivity (irIRN) is detected in the Purkinje cells of the cerebellum in rats and mice (17). Double-labeling of cerebellar sections with irisin antiserum and glutamate decarboxylase (GAD) antibody (Chemicon International, Inc., Temecula, CA) showed that nearly all irIRN Purkinje cells are GAD-positive. Retrograde labeling studies by injecting the fluorescence tracer Fluorogold into the vestibular nucleus of the rat medulla demonstrate that a population of these irlRN positive Purkinje cells innervates the vestibular nucleus. These observations provide structural evidence supporting that irisin may function to coordinate the head and trunk movement during exercise (17). In human hypothalamus, irisin immunoreactivity has been detected in paraventricular neurons expressing neuropeptide Y (30). In spinal cord, multipolar neurons in the anterior horn also express FNDC5/irisin immunoreactivity (31). Interestingly, FNDC5/irisin immunoreactivity is present not only in neurons but also in astrocytes and microglia in the brain tissue (31).

Perhaps the most convincing data supporting the presence of irisin in the central nervous system (CNS) comes from the detection of this peptide in human cerebrospinal fluid (CSF) using an enzyme-linked immunoabsorbant assay (ELISA) (Phoenix Europe, Karlsruhe, Germany) assay (30). Whether irisin in the CSF derives locally from its precursor FNDC5 in the brain or systemically from the circulation remains uncertain. Unless the mechanism underlying the cleavage of neuronal FNDC5 is identified, it remains speculative that irisin can be cleaved and released from its precursor FNDC5 in the CNS.

Can circulating irisin be transported across the brain-blood barrier?

Irisin is detectable in the CSF at a concentration 20–25 folds lower than its levels in serum (30). There exists a positive linear correlation between the CFS and serum irisin in human subjects. This correlation is absent in patient with gestational diabetes (GDM). However, CSF irisin levels in GDM patients are significantly higher when compared with non obese pregnant mothers (30). These findings suggest that the detected irisin in CSF may be derived from the periphery and that the blood-brain barrier (BBB) may limit access of irisin in lean and obese states. It is currently unknown what may mediate this active transport mechanism. For an active transport mechanism, it would be critical to demonstrate the presence of irisin receptor on endothelial cells of the choroid plexus. Thus, further studies should aim to identify the irisin receptor and to demonstrate whether irisin could be transported from blood to CSF by receptor-mediated transcytosis.

Does irisin receptor exist?

Initial data showing that irisin stimulates white-to-brown fat conversion have led to the hypothesis that it functions as a myokine to bind and activate an unknown receptor. This concept is supported by analysis of irisin structure and its intracellular signaling. Analysis of the crystal structure and biochemical characterization of the FNDC5 ectodomain, corresponding to the irisin myokine, shows that irisin consists of an N-terminal fibronectin III (FNIII)-like domain attached to a flexible C-terminal tail (14). The FNIII-like domain forms a continuous intersubunit β-sheet dimer. The dimerization of irisin domain may be served as the preformed myokine ligand to activate its receptor. This study provides the first evidence supporting the presence of an unknown membrane receptor which irisin binds to. Studies on the intracellular signaling pathway activated by irisin also suggest the presence of a functional receptor for this molecule in a variety of cells. In the skeletal muscle, irisin has been reported to activate the AMP-activated protein kinase (AMPK)-p38 MAPK signaling (32). Our studies reveal the AMPK-SREBP2 signaling pathway activated by irisin in hepatocytes (33). In H9C2 cardiomyocytes, irisin activates PI3K-AKT and intracellular Ca^{2+} signaling (34). Extracellular signal-related kinase (ERK) signaling pathway has also been reported to be activated by irisin in adipocytes (35), endothelial cells (36), myocytes (35) and osteoblasts (37). In addition, irisin activates STAT3 signaling in cultured H19-7 cells, a mouse hippocampal cell line (23). All these studies suggest the existence of irisin-specific receptor on a wide range of cell types including hippocampal neurons.

Does circulating irisin increase following exercise?

Initially, Boström et al. (14) reported a two-fold increase of circulating irisin in healthy humans after 10 weeks endurance training. Irisin was thus proposed as an exercise responsive myokine. This observation was further supported by other studies in rodents and in some cases in human subjects. However, contradictory findings exist in human adults. A meta-analysis of 12 studies in eight manuscripts has concluded that chronic resistance exercise training leads to a moderate and significant decrement in circulating irisin compared with the control, while endurance exercise training only has a trend (38). These contradictory findings raise great concerns about the relationship between chronic exercise training and circulating irisin among adult human subjects. Emerging evidences have indicated that circulating irisin may be significantly related with age (39), sex (40) and body mass index (41). Thus, future studies require more well-designed randomized trials that control different exercise training modes, dietary or energy intake, weight loss, as well as changes of body fat percentage or insulin sensitivity following chronic exercise training.

Is irisin the sole peptide released from FNDC5?

Since its discovery in 2012, the existence of irisin has been the subject of debate. The antibody used in Boström's study is not specific for the irisin amino acid sequence. Instead, it covers a segment of FNDC5 sequence distinct from irisin. Evidence for circulating irisin in existing literature is largely based on commercial ELISA kits which are based on polyclonal antibodies (pAbs) not previously tested for cross-reacting with other serum proteins. Analysis of four commercial pAbs by Albrecht et al. showed no immune-reactive bands of the expected size in any biological samples using recombinant glycosylated and non-glycosylated irisin as positive controls. This study casts a doubt on the presence of irisin as a sole peptide released from *Fndc5* (42). A new study by the group that first identified irisin has recently reported a strong piece of evidence favoring irisin as a true circulating peptide (43). By using liquid chromatography-tandem mass spectrometry,

Jedrychowski et al. have identified and quantified the irisin in blood. Further, they have determined that circulating irisin levels in a group of young and healthy volunteers subjected to aerobic training are significantly higher than that in a group of sedentary controls. Thus, more studies are required to verify the existence of irisin.

Future development

One major challenge for future advances in the understanding of irisin biology is identification of its cellular receptor. Further, gain- or loss-of-function models will be important to further assess the physiological function of irisin. Genetic mouse models with conditional ablation of *Fndc5* could unravel new, key biological functions for irisin. Lastly, a specific ELISA kit for irisin is urgently needed. These future studies will be critical for the clarification of presence of circulating irisin and its physiological functions.

Summary

In summary, FNDC5/irisin are present in various regions of the brain. As a neurotrophic factor, irisin is involved in the regulation of neural differentiation and proliferation, neurobehavior, energy expenditure and cardiac function. In addition, irisin may serve as an important cross-organ messenger linking brain with skeletal muscle, adipose tissue and the cardiovascular system to coordinate the beneficial effects of exercise. Future studies should aim at the identification of the yet unknown irisin receptor, development of a reliable irisin assay, genetic manipulation of irisin or its receptor, pharmacological intervention of irisin and its signaling system.

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References

1. Paillard T, Rolland Y, de SoutoBarreto P. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: a narrative review. J Clin Neurol 2015; 11: 212–9.
2. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001; 58: 498–504.
3. Stummer W, Weber K, Tranmer B, Baethmann A, Kempski O. Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. Stroke 1994; 25: 1862–9.
4. Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci 2001; 21: 5678–84.
5. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc Natl Acad Sci USA 1990; 87: 5568–72.
6. Isaacs KR, Anderson BJ, Alcantara AA, Black JE, Greenough WT. Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. J Cereb Blood Flow Metab 1992; 12: 110–9.
7. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci USA 1999; 96: 13427–31.
8. Young D, Lawlor PA, Leone P, Dragunow M, During MJ. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. Nat Med 1999; 5: 448–53.
9. Escorihuela RM, Tobeña A, Fernández-Teruel A. Environmental enrichment and postnatal handling prevent spatial learning deficits in aged hypoemotional (Roman high-avoidance) and hyperemotional (Roman low-avoidance) rats. Learn Mem 1995; 2: 40–8.
10. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002; 25: 295–301.
11. Duman RS. Neurotrophic factors and regulation of mood: role of exercise, diet and metabolism. Neurobiol Aging 2005; 26: 88–93.
12. Mueller K, Möller HE, Horstmann A, Busse F, Lepsien J, Blüher M, Stumvoll M, Villringer A, Pleger B. Physical exercise in overweight to obese individuals induces metabolic- and neurotrophic-related structural brain plasticity. Front Hum Neurosci 2015; 9: 372.
13. Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, Lin JD, Greenberg ME, SpiegelmanBM. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab 2013; 18: 649–59.
14. Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Højlund K, Gygi SP, Spiegelman BM. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012; 481: 463–8.
15. Ferrer-Martínez A, Ruiz-Lozano P, Chien KR. Mouse PeP: a novel peroxisomal protein linked to myoblast differentiation and development. Dev Dyn 2002; 224: 154–67.
16. Teufel A, Malik N, Mukhopadhyay M, Westphal H. Frcp1 and Frcp2, two novel fibronectin type III repeat containing genes. Gene 2002; 297: 79–83.
17. Dun SL, Lyu RM, Chen YH, Chang JK, Luo JJ, Dun NJ. Irisin-immunoreactivity in neural and non-neural cells of the rodent. Neuroscience 2013; 240: 155–62.
18. Tiano JP, Springer DA, Rane SG. SMAD3 negatively regulates serum irisin and skeletal muscle FNDC5 and peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) during exercise. J Biol Chem 2015; 290: 7671–84.
19. Ostadsharif M, Ghaedi K, Hossein Nasr-Esfahani M, Mojbafan M, Tanhaie S, Karbalaie K, Baharvand H. The expression of

peroxisomal protein transcripts increased by retinoic acid during neural differentiation. Differentiation 2011; 81: 127–32.
20. Hashemi MS, Ghaedi K, Salamian A, Karbalaie K, Emadi-Baygi M, Tanhaei S, Nasr-Esfahani MH, Baharvand H. Fndc5 knockdown significantly decreased neural differentiation rate of mouse embryonic stem cells. Neuroscience 2013; 231: 296–304.
21. Forouzanfar M, Rabiee F, Ghaedi K, Beheshti S, Tanhaei S, ShoarayeNejati A, JodeiriFarshbaf M, Baharvand H, Nasr-Esfahani MH. Fndc5 overexpression facilitated neural differentiation of mouse embryonic stem cells. Cell Biol Int 2015; 39: 629–37.
22. Hosseini Farahabadi SS, Ghaedi K, Ghazvini Zadegan F, Karbalaie K, Rabiee F, Nematollahi M, Baharvand H, Nasr-Esfahani MH. ERK1/2 is a key regulator of Fndc5 and PGC1α expression during neural differentiation of mESCs. Neuroscience 2015; 297: 252–61.
23. 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: 1131–6.
24. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci 2013; 14: 7–23.
25. Kuipers SD, Bramham CR. Brain-derived neurotrophic factor mechanisms and function in adult synaptic plasticity: new insights and implications for therapy. Curr Opin Drug Discov Dev 2006; 9: 580–6.
26. Zhang W, Chang L, Zhang C, Zhang R, Li Z, Chai B, Li J, Chen E, Mulholland M. Irisin: a myokine with locomotor activity. Neurosci Lett 2015; 595: 7–11.
27. Zhang W, Chang L, Zhang C, Zhang R, Li Z, Chai B, Li J, Chen E, Mulholland M. Central and peripheral irisin differentially regulate blood pressure. Cardiovasc Drugs Ther 2015; 29: 121–7.
28. Brailoiu E, Deliu E, Sporici RA, Brailoiu GC. Irisin evokes bradycardia by activating cardiac-projecting neurons of nucleus ambiguus. Physiol Rep 2015; 3: e12419.
29. Polyzos SA, Mathew H, Mantzoros CS. Irisin: a true, circulating hormone. Metabolism 2015; 64: 1611–8.
30. Piya MK, Harte AL, Sivakumar K, Tripathi G, Voyias PD, James S, Sabico S, Al-Daghri NM, Saravanan P, Barber TM, Kumar S, Vatish M, McTernanPG. The identification of irisin in human cerebrospinal fluid: influence of adiposity, metabolic markers, and gestational diabetes. Am J Physiol Endocrinol Metab 2014; 306: E512–8.
31. Albayrak S, Atci İB, Kalayci M, Yilmaz M, Kuloglu T, Aydin S, Kom M, Ayden O, Aydin S. Effect of carnosine, methylprednisolone and their combined application on irisin levels in the plasma and brain of rats with acute spinal cord injury. Neuropeptides 2015; 52: 47–54.
32. Lee HJ, Lee JO, Kim N, Kim JK, Kim HI, Lee YW, Kim SJ, Choi JI, Oh Y, Kim JH, Suyeon-Hwang, Park SH, Kim HS. Irisin, a novel myokine, regulates glucose uptake in skeletal muscle cells via AMPK. Mol Endocrinol 2015; 29: 873–81.
33. Tang H, Yu R, Liu S, Huwatibieke B, Li Z, Zhang W. Irisin inhibits hepatic cholesterol synthesis via AMPK-SREBP2 signaling. E BioMedicine 2016; 6: 139–48.
34. Xie C, Zhang Y, Tran TD, Wang H, Li S, George EV, Zhuang H, Zhang P, Kandel A, Lai Y, Tang D, Reeves WH, Cheng H, Ding Y, Yang LJ. Irisin controls growth, intracellular Ca^{2+} signals, and mitochondrial thermogenesis in cardiomyoblasts. PLoS One 2015; 10: e0136816.
35. Huh JY, Dincer F, Mesfum E, Mantzoros CS. Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans. Int J Obes (Lond) 2014; 38: 1538–44.
36. Wu F, Song H, Zhang Y, Zhang Y, Mu Q, Jiang M, Wang F, Zhang W, Li L, Li H, Wang Y, Zhang M, Li S, Yang L, Meng Y, Tang D. Irisin induces angiogenesis in human umbilical vein endothelial cells in vitro and in zebrafish embryos in vivo via activation of the ERK signaling pathway. PLoS One 2015; 10: e0134662.
37. Colaianni G, Cuscito C, Mongelli T, Pignataro P, Buccoliero C, Liu P, Lu P, Sartini L, Di Comite M, Mori G, Di Benedetto A, Brunetti G, Yuen T, Sun L, Reseland JE, Colucci S, New MI, Zaidi M, Cinti S, Grano M. The myokine irisin increases cortical bone mass. Proc Natl Acad Sci USA 2015; 112: 12157–62.
38. Qiu S, Cai X, Sun Z, Schumann U, Zügel M, Steinacker JM. Chronic exercise training and circulating irisin in adults: a meta-analysis. Sports Med 2015; 45: 1577–88.
39. Kim HJ, So B, Choi M, Kang D, Song W. Resistance exercise training increases the expression of irisin concomitant with improvement of muscle function in aging mice and humans. Exp Gerontol 2015; 70: 11–7.
40. Kerstholt N, Ewert R, Nauck M, Spielhagen T, Bollmann T, Stubbe B, Felix SB, Wallaschofski H, Gläser S, Friedrich N. Association of circulating irisin and cardiopulmonary exercise capacity in healthy volunteers: results of the Study of Health in Pomerania. BMC Pulm Med 2015; 15: 41.
41. Kim H, Lee HJ, So B, Son JS, Yoon D, Song W. Effect of aerobic training and resistance training on circulating irisin level and their association with change of body composition in overweight/obese adults: a pilot study. Physiol Res 2015. [Epub ahead of print].
42. Albrecht E, Norheim F, Thiede B, Holen T, Ohashi T, Schering L, Lee S, Brenmoehl J, Thomas S, Drevon CA, Erickson HP, Maak S. Irisin–a myth rather than an exercise-inducible myokine. Sci Rep 2015; 5: 8889.
43. Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS, Gygi SP, Spiegelman BM. Detection and quantitation of circulating human irisin by tandem mass spectrometry. Cell Metab 2015; 22: 734–40.