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Review Article

The Protective Actions of Exercise on Bone Formation, the Relationship between FNDC5/ Irisin and Autophagy

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Abstract

Most researchers have recognized the beneficial effects of exercise on bone formation in the organism. Irisin released from muscles is considered to be the link between muscles and other organs, and its main function is to change subcutaneous and visceral adipose tissue into brown adipose tissue, with a consequent increase in thermogenesis. Irisin can regulate glucose metabolism, bone metabolic homeostasis, and systemic inflammatory response. Moreover, it has become the focus of more and more research in fatty acid oxidation and hepatic glucose xenogenesis. Autophagy, as a conserved material recycling pathway, can effectively degrade and reuse cellular proteins and organelles. In addition, autophagy extensively affects cellular metabolism and function. However, the role of autophagy in the biological effect of irisin has not been fully reviewed. The focus of this short review is to gather the latest knowledge of irisin and autophagy in bone metabolism and related cell signaling pathways, and provide the potential regulation of irisin on autophagy.

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Introduction

Recently, there has been an increasing interest in the osteoprotective effects of exercise. Sedentary or inactivity is considered an independent risk factor for many diseases, such as atherosclerosis, insulin resistance, dyslipidemia and heart disease. Lack of exercise is considered an independent risk factor for many diseases, such as atherosclerosis, insulin resistance, dyslipidemia and heart disease [1]. In the Netherlands, the prevalence of overweight (obesity) was 9.2-17.3% (2.5-4.3%) for boys and 14.6%-24.6% (2.3-6.5%) for girls [2]. Irisin, a muscle factor released by skeletal muscle during exercise, is a type I transmembrane glycoprotein encoded by the Fibronectin Type III Domain-Containing protein 5 (FNDC5) gene, and its biological activity is regulated by the peroxisome proliferator-activated receptor γ co-stimulator 1a (peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α) is regulated [3]. The current study found that FNDC5 is widely distributed, including in skeletal muscle, cardiac muscle, adipose tissue, liver, brain, bone, pancreas, kidney and ovary, and is expressed at different levels in each tissue. In adipose tissue, the expression of irisin is only 5% of that in skeletal muscle cells, and the level of secretion in subcutaneous adipose tissue is lower than that in visceral adipose tissue [4]. It has been noted that in adult mice FNDC5 is mainly distributed in brain, heart and skeletal muscle tissues [5]. In adults, on the other hand, FNDC5 is highly expressed in muscle, pericardium and rectum, while it is expressed at lower levels in brain, kidney, liver, lung and adipose tissues [6].

Current studies have shown that the endocrine function of irisin not only acts on skeletal muscle itself, but also regulates the utilization of skeletal muscle for substances such as sugar and protein. It reaches all parts of the peripheral body through blood circulation and performs messenger functions between skeletal muscle and peripheral tissues, participating in the regulation of glucose uptake, fatty acid oxidation, hepatic gluconeogenesis and lipolysis in peripheral tissues [7]. In the circulation, the level of irisin are positively correlated with a variety of factors, including BMI, blood glucose, and insulin-like growth factors, but negatively correlated with factors including age, insulin, and triglycerides [6]. In addition, irisin improved insulin resistance by increasing Peroxisome Proliferator-Activated Receptor α (PPAR-α) and inhibiting hyperglycemic toxicity, enhancing Glucose Transporter Type 4 (GLUT4) translocation in muscle as well as in adipose tissue [3]. Irisin also up regulated the expression of Uncoupling Protein 1 (UCP1) in adipose tissue mitochondria, induces the formation of adipose droplets, leading to increased oxygen consumption in adipocytes, and eventually the regulation of cellular energy metabolism [8]. Moreover, in human hepatocellular carcinoma cells, mice and human primary hepatocytes, and diabetic mice, Irisin modulates glucose homeostasis and improves abnormal glucose tolerance and insulin sensitivity by activating the phosphatidylinositol 3-kinase/protein kinase (PI3K) and Adenosine Monophosphate (AMP)-Activated Protein Kinase (AMPK) signaling pathways, thereby inhibiting the development of obesity and insulin resistance [9,10]. These results suggest that irisin is not only a muscle factor but also an adipokine, which involved in complex metabolic regulation by autocrine and paracrine means.

At present, many researches have shown that hypermobility is positively associated with bone loss and a significantly increased risk of fracture [11]. However, it has also been reported that reduced exercise did not alter bone mass but significantly increased fracture risk [12]. In postmenopausal women, the higher the skeletal muscle content, the higher the bone mineral density, and the lower the risk of fracture [13]. Findings from a recent study have shown that exercise-induced-irisin as a messenger of the interconnection between skeletal muscle and bone tissue. After running wheel exercise, the expression level of irisin were significantly increased compared to mice without exercise [14]. Moreover, exercise induced osteogenic differentiation of osteoblasts and increased the expression of alkaline phosphatase and type I collagen in osteoblasts. Storlino et al., reported that in osteoid cells, the expression level of sclerosteosis (SOST) was downregulated after intermittent administration of irisin, which is a negative regulator of bone formation [15]. Similarly, Colaiannia et al., also reported that recombinant irisin significantly increased cortical bone mass in mice, and speculated that recombinant irisin might be a novel drug for the treatment of osteoporosis, sarcopenia, and metabolic syndrome [16]. Irisin also improved the geometry and strength of cortical bone, especially the density of bone trabeculae. Mechanistically, irisin increased bone marrow stromal cell differentiation to mature osteoblasts through activation of the Wnt/β-catenin pathway [14] and inhibits osteoclast differentiation through the Bone Morphogenetic Protein (BMP) receptor signaling pathway [17]. In addition, irisin increased bone mineralization by upregulating the expression level of Osteopontin (OPN), which is a component of the bone extracellular matrix and a key regulator of bone tissue mineralization [18]. Furthermore, irisin can also stimulate osteoblast proliferation, differentiation and increase Alkaline Phosphatase (ALP) activity through p38/MAPK and ERK pathways. In contrast, the osteogenic effects of irisin were reversed after inhibition of p38/MAPK and ERK signaling pathways [19]. In osteoclast, irisin also inhibited the expression of Receptor Activator of Nuclear Kappa-B Ligand (RANKL) and nuclear factor of activated T cells cytoplasmic 1 (NFATc1) [20]. Clinical studies have shown that the levels of Irisin in human circulation are negatively correlated with the SOST, and ultimately inhibit the Wnt signaling pathway and downregulates bone formation [21]. In addition, compared to normal people, the level of irisin are significantly lower in patients with osteoporosis. Even after correcting for BMI, BMD and serum vitamin D levels, this effect continues [22]. These animal experiments and clinical studies have confirmed that the skeletal muscle secreted myokine, irisin, exerts a positive influence on bone tissue metabolism through molecular mediation *in vivo*.

Cellular autophagy, also known as type II programmed cell death, is the degradation by cells of their own damaged and senescent macromolecules, such as cytoplasm, organelles and protein multimers, through lysosomes under the influence of external environmental factors. The occurrence of autophagy requires the wrapping of cellular debris by bilayer membrane structures to form autophagosomes, which then bind to autophagolysosomes to degrade and recycle the contents to produce new proteins and organelles [23]. Under stress, autophagy is activated to degrade intracellular components, remove damaged organelles, and limit further expansion of damage [24]. However, excessive activation of autophagy can lead to the breakdown of a large number of essential molecules and organelles within the cell, which can induce cell death [25]. The process of autophagy can be divided into multiple steps, including induction, cargo recognition and screening, vesicle formation, autophagosome-lysosome fusion, degradation, and release of products. Depending on the pathway of species transport to the lysosome, autophagy is classified into macroautophagy, microautophagy, and Chaperone-Mediated Autophagy (CMA) [26]. Macroautophagy, which is used to degrade long-lived cytoplasmic proteins and functionally abnormal organelles, decreases in level with increasing age, leading to the accumulation of waste products associated with cellular aging and further aggravating the aging process [27]. Throughout the autophagy process, many related molecules are involved, such as autophagy-associated gene (Atg) proteins and Vacuolar sorting Proteins (Vps). In mechanism, the Vps34-Vpsl5-Beclinl complex is required for omegasome formation. Moreover, the Atg5-Atgl2-Atgl6 complex promotes the activation and localization of light chain 3 (LC3). After that, the autophagosome fuses with the lysosome to form an autophagic lysosome that breaks down the material to be degraded. Microautophagy is degraded by direct invagination of the lysosomal membrane, which directly isolates and wraps the phagocytic cytoplasmic component [28]. CMA is found only in mammalian cells, it forms a molecular chaperone-substrate complex through the molecular chaperone HSC70 recognition-specific consensus sequence (KFERQ), which then binds to Lysosome-Associated Membrane Protein 2A (LAMP-2A) for selective transport to lysosomes and reused by hydrolases [29].

At present, autophagy, as a newly discovered metabolic modality, widely regulates the synthesis, degradation, and energy metabolism of various cellular substances and actively regulates the aging process of the organism. A growing number of studies have shown that appropriate physical exercise is beneficial to health. Besides, exercise is considered as a non-pharmacological treatment modality for several diseases, such as metabolic diseases, cardiovascular diseases, and neurological diseases [30,31,32]. It has been reported that regular physical exercise is effective in increasing the level of autophagy in adipose tissue, heart, liver, pancreatic cells, peripheral blood mononuclear cells (PBMC) and brain [33,34]. Similarly, Grumati et al., reported that ultra-endurance exercise significantly increased autophagy levels through LC3a to LC3b conversion in skeletal muscle [35]. Furthermore, in Parkinson's disease and Huntington's disease, autophagy is able to degrade cellular aggregates closely associated with the disease, such as α-synuclein and Huntington's mutants. Moreover, autophagy is also closely associated with mitochondrial biogenesis, endurance enhancement and angiogenesis. In mechanism, the PI3K/Akt/mTOR signaling pathway is the main regulatory channel of autophagy, including phosphorylated PI3K, activated protein kinase B (Akt/PKB), and downstream target of rapamycin protein (mTOR). In terms of energy metabolism, He et al., reported that autophagy-deficient mice exhibit impaired glucose uptake, GLUT4 translocation and AMPK activation during acute exercise [33].

In vivo, autophagy plays an important role in the molecular mechanism of exercise-induced irisin. Irisin was able to significantly reduce insulin resistance through regulation mediated by autophagy in mice. Ye et al., also reported that irisin improved mitochondrial respiration and function to increase autophagy levels via p38-MAPK-PGC-1α pathway. They also noted that irisin significantly increased the expression level of LC3 and increased the degradation of p62 in

a dose-dependent manner [36]. Furthermore, in mouse and human liver, irisin increased hepatic glycogen and reduced gluconeogenesis by activating PI3K/Akt and AMPK [9,10]. In contrast, in FNDC5-/- mice, primary hepatocytes show lower levels of autophagy and fatty acid oxidation is also inhibited, culminating in mice with severe hepatic steatosis. In contrast, after treatment with rapamycin, the mTOR was inhibited, autophagy and fatty acid oxidation (FAO) levels were upregulated, and hepatic steatosis was significantly improved [37].

Although the relationship between irisin and autophagy is not fully understood, related studies have indicated that exercise can regulate autophagy levels in skeletal muscle [38] and liver [33]. Acute exercise activates autophagy through post-translational modifications and can activate autophagy more chronically through the involvement of transcriptional programs [34]. A single bout of endurance exercise can increase the expression of autophagy-related gene, and ultimately lead to a long-term adaptive response. In mechanism, exercise can alter skeletal muscle energy metabolism and promote mitochondrial biosynthesis, participate in skeletal muscle quality control, modulate inflammatory responses and inhibit muscle atrophy by regulating the AMPK signaling pathway. PGC-1α/β overexpression inhibits muscle protein degradation, induction of ubiquitin ligases, and disuse atrophy [39,40]. Moreover, exercise also induces autophagy through the Akt/mTOR and Akt/FoxO3a signaling pathways, inhibits E3 ubiquitin ligases in aged skeletal muscle, and alleviates sarcopenia [41]. Previous studies reported that PGC-1α is required for LC3 regulation in skeletal muscle of adult mice after acute exercise and exercise training [42]. Furthermore, it has been shown that high-fat and high-sucrose diets play a role in muscle dysfunction by regulating autophagy, and exercise can alter the expression levels of autophagy-related proteins [43]. These studies support that exercise-induced irisin is closely related to the occurrence of autophagy.

In conclusion, the health-promoting effects of exercise have been well known, and irisin as an exercise-induced muscle factor has been shown to play a protective role against many metabolism-related diseases, such as diabetes and cardiovascular disease. Recently, irisin has been shown to play an important role in the regulation of autophagy in a variety of cells, including myofibers, cardiomyocytes, hepatocytes and pancreatic cells. Moreover, AMPK signaling pathway, Akt/mTOR and Akt/FoxO3a signaling pathways play a key role in the induction and regulation of autophagy. As we reviewed, these new important evidences help us to clarify the beneficial effects of exercise-induced irisin on the organism through autophagic pathways, especially for bone-related diseases. However, despite the very strong appeal of irisin, a large number of studies are still needed to understand the relationship between irisin and autophagy and disease at the molecular level. In addition, its receptor deserves to be further investigated in order to elucidate the mechanism of action of irisin in more detail.

References

1. Booth FW, Roberts CK, Laye MJ (2012) Lack of exercise is a major cause of chronic diseases. Compr Physiol 2: 1143-1211.
2. Schokker DF, Visscher TLS, Nooyens ACJ, van Baak MA, Seidell JC (2007) Prevalence of overweight and obesity in the Netherlands. Obes Rev 8: 101-107.
3. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, et al. (2012) A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481: 463-468.
4. Norheim F, Langleite TM, Hjorth M, Holen T, Kielland A, et al. The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. FEBS J 281: 739-749.
5. Teufel A, Malik N, Mukhopadhyay M, Westphal H (2002) Frcp1 and Frcp2, two novel fibronectin type III repeat containing genes. Gene 297: 79-83.
6. Huh JY, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, et al. (2012) FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. m RNA expression and circulating concentrations in response to weight loss and exercise. Metabolism 61: 1725-1738.
7. Pedersen BK, Febbraio MA (2012) Muscles, exercise and obesity: skeletal muscle as a secretory organ[J]. Nat Rev Endocrinol 8: 457-465.
8. Wu J, Boström P, Sparks LM, Ye L, Choi JH, et al. (2012) Beige Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human. Cell 150: 366-376.
9. Liu TY, Shi CX, Gao R, Sun HJ, Xiong XQ, et al. (2015)Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes. Clin Sci (Lond) 129: 839-850.
10. Xin C, Liu J, Zhang J, Zhu D, Wang H, et al. (2016) Irisin improves fatty acid oxidation and glucose utilization in type 2 diabetes by regulating the AMPK signaling pathway. Int J Obes (Lond) 40: 443-451.
11. Oppl B, Michitsch G, Misof B, Kudlacek S, Donis J, et al. (2014) Low Bone Mineral Density and Fragility Fractures in Permanent Vegetative State Patients. J Bone Miner Res 29: 1096-1100.
12. Epstein S, Inzerillo AM, Caminis J, Zaidi M (2003) Disorders associated with acute rapid and severe bone loss. J Bone Miner Res 18: 2083-2094.
13. Lombardi G, Sanchis-Gomar F, Perego S, Sansoni V (2016) Implications of exercise-induced adipo-myokines in bone metabolism. Endocrine 54: 284-305.
14. Colaianni G, Cuscito C, Mongelli T, Oranger A, Mori G, et al. (2014) Irisin enhances osteoblast differentiation in vitro. Int J Endocrinol 2014: 902186.
15. Storlino G, Colaianni G, Sanesi L, Lippo L, Brunetti G, et al. (2020) Irisin Prevents Disuse-Induced Osteocyte Apoptosis. J Bone Miner Res 35: 766-775.
16. Colaianni G, Cuscito Concetta, Mongelli T, Pignataro P, Buccoliero C, et al. (2015) The myokine irisin increases cortical bone mass. Proc Natl Acad Sci U S A 112: 12157-12162.
17. Zhang Y, Xie C, Wang H, Foss RM, Clare M, et al. (2016) Irisin exerts dual effects on browning and adipogenesis of human white adipocytes. Am J Physiol Endocrinol Metab 311: 530-541.
18. Wesson JA, Richard JJ, Mazzali M, Beshensky AM, Stietz S, et al. (2003) Osteopontin is a critical inhibitor of calcium oxalate crystal formation and retention in renal tubules. J Am Soc Nephrol 14: 139-147.
19. Qiao X, Nie Y, Ma Y, Chen Y, Cheng R, et al. (2016) Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways. Scientific reports 6: 1-12.
20. Kaji H (2016) Effects of myokines on bone. BoneKey reports 5: 826.
21. Colaianni G, Notarnicola A, Sanesi L, Brunetti G, Lippo L, et al. (2017) Irisin levels correlate with bone mineral density in soccer players. J Biol Regul Homeost Agents 31: 21-28.

22. Anastasilakis AD, Polyzos SA, Makras P, Gkiomisi A, Bisbinas I, et al. (2014) Circulating irisin is associated with osteoporotic fractures in postmenopausal women with low bone mass but is not affected by either teriparatide or denosumab treatment for 3 months. Osteoporos Int 25: 1633-1642.

23. Yang Z, Klionsky DJ (2010) Eaten alive: a history of macroautophagy. Nature cell biology 12: 814-822.

24. Mizushima N, Levine B, Cuervo AM, Klionsky DJ (2008) Autophagy fights disease through cellular self-digestion. Nature 451: 1069-1075.

25. Kroemer G, Levine B (2008) Autophagic cell death: the story of a misnomer. Nat Rev Mol Cell Biol 9: 1004-1010.

26. Ravikumar B, Sarkar S, Davies JE, Futter M, Garcia-Arencibia M, et al. (2010) Regulation of mammalian autophagy in physiology and pathophysiology. Physiol Rev 90: 1383-1435.

27. Huber TB, Edelstein CL, Hartleben B, Inoki K, Jiang M, et al. (2012) Emerging role of autophagy in kidney function, diseases and aging. Autophagy 8: 1009-1031.

28. Declèves AE, Sharma K, Satriano J (2014) Beneficial effects of AMP-activated protein kinase agonists in kidney ischemia-reperfusion: autophagy and cellular stress markers. Nephron Exp Nephrol 128: 98-110.

29. Majeski AE, Dice JF (2004) Mechanisms of chaperone-mediated autophagy. Int J Biochem Cell Biol 36: 2435-2444.

30. Dunstan D (2011) Exercise and T2DM-move muscles more often!. Nat Rev Endocrinol 7: 189-190.

31. Lee CD, Folsom AR, Blair SN (2003) Physical activity and stroke risk: a meta-analysis. Stroke 34: 2475-2481.

32. Vinereanu D (2006) Risk factors for atherosclerotic disease: present and future. Herz 3: 5-24.

33. He C, Bassik MC, Moresi V, Sun K, Wei Y, et al. (2012) Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. Nature 481: 511-515.

34. Vainshtein A, Hood DA (2016) The regulation of autophagy during exercise in skeletal muscle. J Appl Physiol 120: 664-673.

35. Grumati P, Coletto L, Schiavinato A, Castagnaro S, Bertaggia E, et al. (2011) Physical exercise stimulates autophagy in normal skeletal muscles but is detrimental for collagen VI-deficient muscles. Autophagy 7: 1415-1423.

36. Ye X, Shen Y, Ni C, Ye J, Xin Y, et al. (2019) Irisin reverses insulin resistance in C2C12 cells via the p38-MAPK-PGC-1 pathway. Peptides 119: 170120.

37. Liu TY, Xiong XQ, Ren XS, Zhao MX, Shi CX, et al. (2016) FNDC5 alleviates hepatosteatosis by restoring AMPK/mTOR-mediated autophagy, fatty acid oxidation, and lipogenesis in mice. Diabetes 65: 3262-3275.

38. Halling JF, Ringholm S, Nielsen MM, Overby P, Pilegaard H (2016) PGC-1alpha promotes exercise-induced autophagy in mouse skeletal muscle. Physiol Rep 4: 12698.

39. Brault JJ, Jespersen JG, Goldberg AL (2010) Peroxisome proliferator-activated receptor gamma coactivator 1alpha or 1beta overexpression inhibits muscle protein degradation, induction of ubiquitin ligases, and disuse atrophy. J Biol Chem 285: 19460-19471.

40. Drake JC, Wilson RJ, Yan Z (2016) Molecular mechanisms for mitochondrial adaptation to exercise training in skeletal muscle FASEB J 30: 13-22.

41. Zeng Z, Liang J, Wu L, Zhang H, Lv J, et al. (2020) Exercise-Induced Autophagy Suppresses Sarcopenia Through Akt/mTOR and Akt/FoxO3a Signal Pathways and AMPK-Mediated Mitochondrial Quality Control. Front Physiol 11: 583478.

42. Brandt N, Nielsen L, Thiellesen BB, Gudiksen A, Ringholm S, et al. (2018) Impact of beta-adrenergic signaling in PGC-1alpha-mediated adaptations in mouse skeletal muscle. Am J Physiol Endocrinol Metab 314: 1-20.

43. Zhang D, Lee JM, Kwak SE, Shin HE, Zhang Y, et al. (2019) Effect of a Single Bout of Exercise on Autophagy Regulation in Skeletal Muscle of High-Fat High-Sucrose Diet-Fed Mice. J Obes Metab Syndr 28: 175-185.

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