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Review Article

Irisin/FNDC5: A Novel Player in Musculoskeletal Health

Sreedevi Behera[1], Jyotirmaya Behera[1*]

[1]Bone Biology Laboratory, Department of Physiology, School of Medicine, University of Louisville, Louisville, KY 40202, USA.

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***Corresponding author:** Behera J, Bone Biology Laboratory, Department of Physiology, School of Medicine, University of Louisville, Louisville, KY 40202, USA. E-mail: j0behe02@louisville.edu

Abstract

Osteoporosis is a major health problem that affects mainly aging and postmenopausal women and is characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility. Emerging shreds of evidence suggested that physical exercise has a beneficial effect on bone loss/osteoporosis. Irisin is a novel hormone-like myokine that was reported in 2012 and proposed to be produced in abundance by skeletal muscle as well as bone tissue in response to exercise. The studies have provided shreds of evidence that irisin can promote osteoblast differentiation, mineralization and increases bone mass and mechanical strength, and geometry in mice. We also review the autocrine effects of irisin in skeletal muscle, in which it upregulates expression of several pro-myogenic and exercise response genes in skeletal muscle including the expression of its precursor (FNDC5). In this review, we emphasize the structure and function of irisin and its functional role in skeletal homeostasis as well as skeletal muscle mass and regeneration. Further, the review narrates the future efficacy of irisin restoring the bone and reversing muscle wasting and could be developed as an irisin-based therapy for physically weaken and osteoporosis patients.

Keywords: FNDC5/irisin; Muscle function; Skeletal loss; Osteogenesis; Hind-limb unloading

Introduction

Osteoporosis, is a systemic and progressive bone disease and characterized by a low bone mass due to increased osteoclastic bone resorption and/or reduced osteoblastic bone formation with the occurrence of spontaneous fractures [1, 2]. A recent study was reported that physical activity was known to benefit several metabolic diseases, such as obesity, diabetes, fatty liver disease, osteoporosis, and age-related muscle wasting [3, 4, 5]. It is also widely evidenced that muscle and bone are intimately worked together in terms of the paracrine and endocrine signals. Various bone-derived signals such as osteocalcin, insulin-like growth factor 1 (IGF-1), prostaglandin E2, and FGF-23 promotes positive effects. However, signals like activin or TGF-β are known to cause negative responses [6, 7]. Likewise, muscle-derived signals like interleukins (IL-6, IL-8, IL-15), indirectly working on the bone and myokines, such as irisin, can directly affect bone metabolism [8-11].

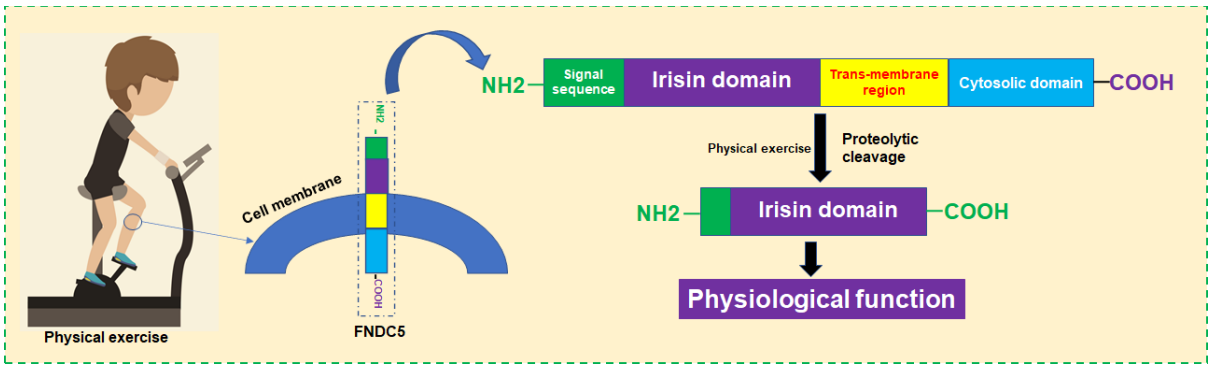
The myokine Irisin is cleavage from its precursor type III domain-containing protein 5 (FNDC5), expressed in skeletal muscle as well as other tissues including bone [12, 10] and released into the bloodstream. Yet it is not known about the

irisin function and binding to its unknown receptor. In 2012, irisin was described as a hormone-like molecule and known to be secreted abundantly by skeletal muscle during physical exercise, which elicits the white adipose tissue (WAT) to adopt a brown adipose tissue-like phenotype through increasing cellular mitochondrial density and expression of uncoupling protein-1 [12]. This study also suggested that irisin could have strong beneficial effects on metabolic diseases. Colaianni et al described that the primary target of irisin is the skeleton than WAT [13]. In this review, we provide a detailed understanding of the role of irisin on bone and indeed has also an additional link in defining bone–muscle cross-talk.

Structure of myokine Irisin and its release

Bostrom et al. 2012, first identified myokine irisin in skeletal muscle under physical exercise [13]. Irisin consists of 112 aa residues and corresponds to the extracellular receptor ectodomain of a type I membrane protein, fibronectin type III domain-containing protein 5 (FNDC5). Following physical exercise, it is cleaved from the FNDC5 and shed into the extracellular milieu and bloodstream (5). Schumacher et al described the crystal structure of the FNDC5. The crystal structure shows that irisin consists of an N-terminal fibronectin III (FNIII)-like domain attached to a flexible C-terminal tail of FNDC5. Interestingly, the FNIII-like domain of irisin forms a continuous intersubunit β-sheet dimer that is connected to a short transmembrane region which is followed by the cytosolic region [14]. It is also reported that mouse, rat, and human irisin are expected to have 100% identical in amino acid sequence [15]. Several factors are indeed involved to generate irisin release in skeletal muscle under physical exercise. The transcriptional coactivator, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), regulates many biological processes involved in energy metabolism and it modulates the factors secreted from skeletal muscle [14]. The work of the Boström et al. demonstrated that FNDC5 is proteolytically cleaved to form the hormone irisin [13] and followed by secreted into the blood [13]. FNDC5/Irisin is also synthesized in various tissues such as the pericardium, heart, brain, and skeleton of different species and was originally discovered as a receptor and shown to critical for cellular differentiation [14].

Figure (1): Structure of FNDC5 and release of myokine Irisin under physical exercise



The domain organization of the FNDC5 receptor is shown on the cell membrane. It contains an N-terminal signal sequence (-NH2), and followed by the irisin domain, which contains an N-terminal FNIII-like region and a flexible C-terminal tail. The irisin domain is connected to a short transmembrane region, which is followed by the cytosolic region (-COOH). The research indicates that following physical exercise, the irisin domain undergoes proteolytic cleavage of mature FNDC5 and is

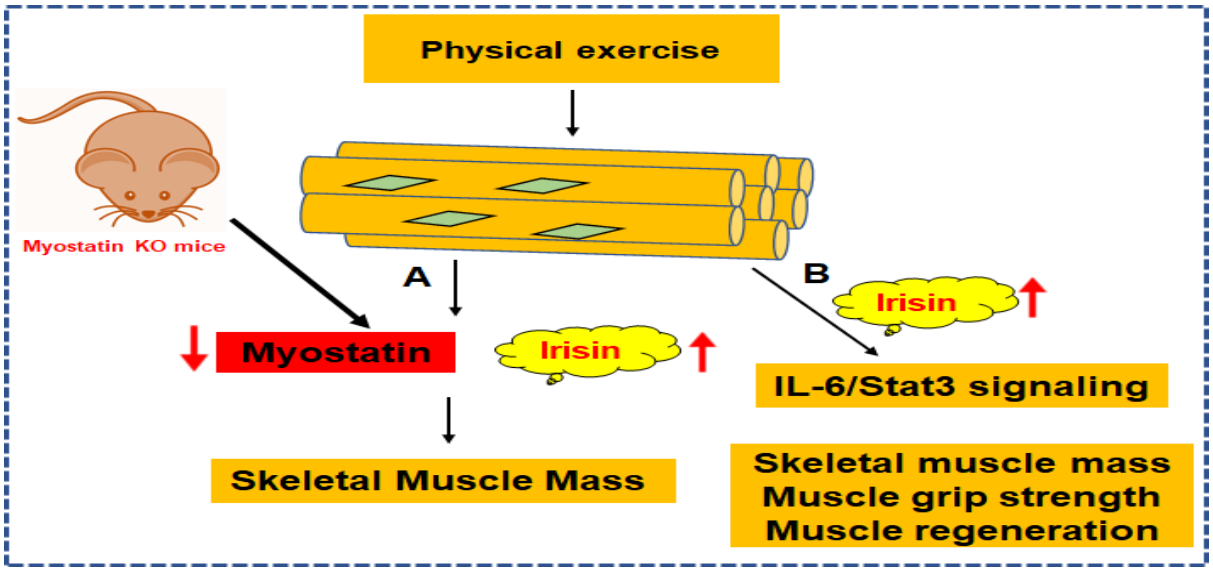
released into extracellular spaces and mediate physiological function in the organism.

The functional role of Irisin on muscle health

It has been reported that physical exercise improves muscle function via myokine irisin [16].

The work of the Reza et al demonstrated that irisin induces expression of several pro-myogenic and exercise response genes in myotubes, myogenic differentiation, and myoblast fusion via activation of IL6 signaling. Injection of irisin in mice improves grip strength of uninjured muscle. In the skeletal muscle injury mouse model, they demonstrate that irisin injection improves regeneration and induces skeletal muscle hypertrophy through activation of satellite cells and enhanced protein synthesis. Additionally, irisin injection increases skeletal muscle mass by enhancing satellite cell activation and reducing protein degradation. Colaianni, G et al., 2015 suggested that healthy mice treated with r-irisin displayed a higher number of FNDC5+ fibers and increased irisin synthesis than mice injected with control in vivo [10]. In support of this finding, other authors showed that C2C12 myotubes treated with r-irisin (3.1–12.4 ng/mL) had observed an increased expression of specific mitochondrial transcription factors, such as PGC-1α, nuclear respiratory factor 1, and mitochondrial transcription factor A (Tfam) and found to increase the mitochondrial content and oxidative phosphorylation [17]. Huh et al., 2014 demonstrate that elevated levels of IGF-1 and low levels of myostatin were observed in human myocytes treated with r-irisin through an ERK-dependent pathway [18]. Indeed, it has been demonstrated that skeletal muscle mass was negatively associated with myostatin expression level [19]. Interestingly, an increased skeletal muscle mass and a higher level of irisin and its precursor were observed in the myostatin knock-out mice model, suggests that the direct relationship between increased muscle mass and irisin synthesis [20] (Figure 2). Others have shown that inhibition of myostatin could promote skeletal muscle mass [21]. The work of Ge et al., 2017 reported that myostatin expression regulates FNDC5/Irisin function through a novel miR-34a-dependent post-transcriptional mechanism in the browning of white adipocytes [22]. Loss or deficiency of myostatin increases irisin level thereby, it enhances the browning of white adipose tissues. These data suggest that irisin functions as a potent pro-myogenic factor in muscle health.

Figure (2): Skeletal irisin promotes skeletal muscle mass and regeneration during physical exercise



A. The proposed mechanism of physical exercise-mediated recovery of skeletal muscle dysfunction via inhibition of myostatin-dependent muscle atrophy. An increased skeletal muscle mass and a higher level of irisin were observed in the mouse model of myostatin deficiency, suggesting that irisin is indispensable for muscle mass.
B. The proposed model of physical exercise-induced skeletal muscle mass and strength. Physical exercise improves skeletal muscle regeneration, strength, and overall muscle health via irisin-dependent IL-6/Stat3 signaling.

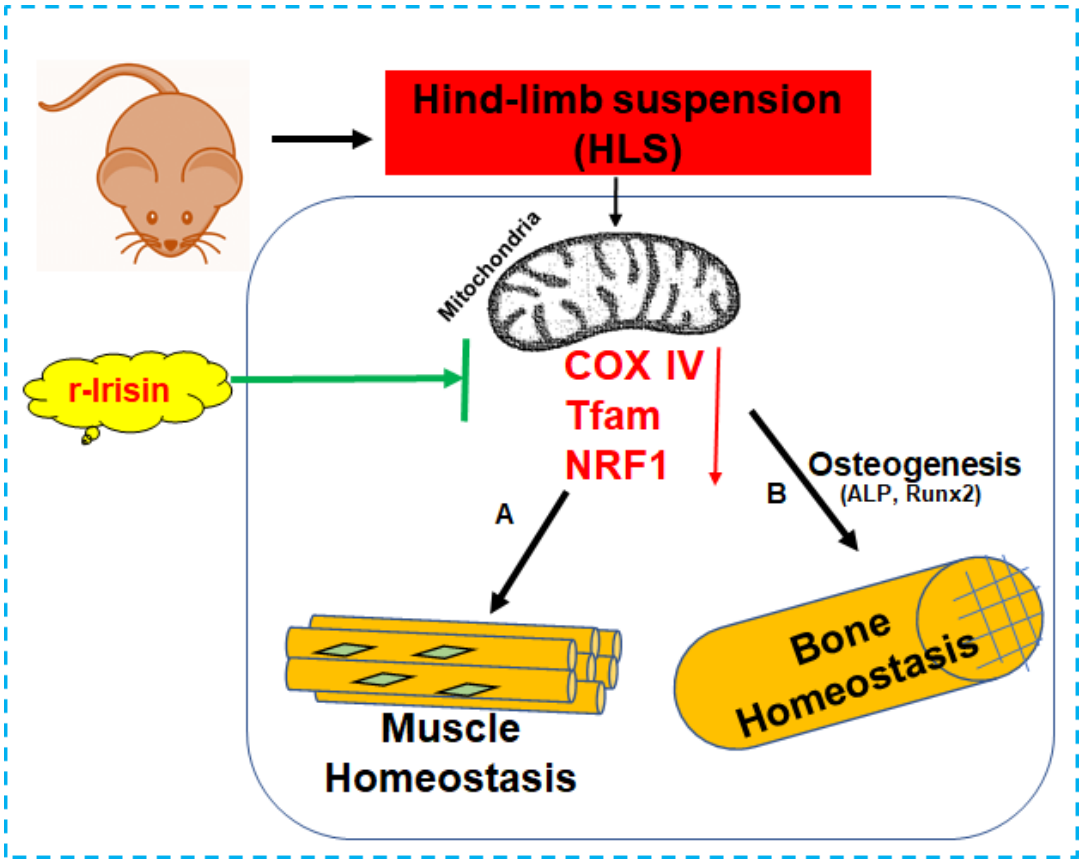
The functional role of Irisin on bone health

It has been recently demonstrated that exercise activity increases the expression of the myokine Irisin in skeletal muscle, which is able to drive the beneficial effects for an organism and could be a potent stimulus for the new bone formation. Colaianni et al., 2014 reported that conditioned medium collected from muscle cells from exercised mice enhanced the osteoblast differentiation from bone marrow-derived stromal cells. They also demonstrate that number of alkaline phosphatase (ALP)+ colonies and mRNA transcript expression of ALP, collagen type I, RUNX2, and osterix were increased upon CM addition to osteoblast cultures, indicating the presence of irisin in the conditioned media from exercised mice [23]. Further, they studied the skeletal effect of the irisin in the healthy and osteoporotic mouse model. Treatment with recombinant irisin to of healthy mice for 4 weeks, improves bone mass and biomechanical properties compared to vehicle-treated mice [10]. They have demonstrated that irisin plays a key role in the early phase of osteoblast differentiation and the late stage of mineralization. Interestingly, these irisin mediated effects are indeed associated with increased mRNA levels of osteogenic transcription factors such as RUNX2, and osterix, as well as the Wnt pathway gene, β-catenin is involved in osteoblast differentiation [10].

The skeletal effect of the irisin is well studied in disuse-induced bone loss mouse model and found to be beneficial on the organism and is a potent stimulus for new bone development. Allen Et al., 2003 reported that administration of irisin partially prevents the disuse-induced osteoporosis and muscular atrophy in "hind-limb suspended" mice, a murine model. They found that simulated resistance exercise mediated irisin increases bone formation more precisely on cortical surfaces [24, 25]. Colaianni et al., 2017 again reported that irisin

administration in hind-limb suspended (HLS) mice, improves cortical and trabecular BMD, bone volume fraction (BV/TV) loss, and Fractal Dimension [26]. The molecular effect of irisin in HLS mice was associated with the reduction of sclerostin and an increase of osteoprotegerin and subjected to an increase in systemic irisin level [26]. Additionally, they have also demonstrated that cytochrome c oxidase subunit I (COX IV), nuclear respiratory factor 1 (NRF1), and mitochondrial transcription factor A (TFAM) expression was indeed improved, indicating it might be improved the mitochondrial dysfunction following irisin administration during musculoskeletal unloading [26] (Figure 3).

Figure (3): Irisin administration prevents the unloading induced musculoskeletal dysfunction



A. The proposed mechanism of irisin-mediated recovery of skeletal muscle dysfunction via reversing the expression of mitochondrial specific COX-IV and Tfam and nuclear respiratory factor 1 (NRF1). The hind-limb suspension (HLS) causes mitochondrial dysfunction via inhibition of COX-IV, Tfam and NRF-1 lead to muscle loss and irisin treatment reverse it.

B. The proposed model of HLS mediated ablation of osteogenesis and bone homeostasis. However, irisin administration restores the bone homeostasis via increased ALP and Runx2 expression.

Conclusions

Given the key findings of irisin in muscle and bone homeostasis, physical exercise could be an effective remedy for maintaining musculoskeletal health. However, further studies would be warranted to study the effectiveness of skeletal irisin on osteoporosis and muscle atrophy in human subjects to assess whether irisin could prevent the disuse or age-related osteoporotic bone loss and muscle wasting. On other hand, molecular understanding of irisin that governs the cellular and molecular pathways in

triggering the development of muscle and bone mass is lacking still lacking and needs to be explored. Therefore, future research could provide a novel mean of the answer to propose for the usage of the irisin as a therapeutic strategy for the prevention and treatment of osteopenia, osteoporosis, sarcopenia, and particularly in those patients with a physical disability and might represent an effective therapeutic measure for an astronaut who subjected to microgravity associated musculoskeletal loss.

Author Contributions

J.B., S.B., conceived the idea and made the manuscript draft; S.B., wrote the manuscript. J.B. provided the novel knowledge on the skeletal irisin, wrote and reviewed the overall manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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