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A review on irisin, a new protagonist that mediates muscle–adipose–bone–neuron connectivity

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Abstract. – Physical activity improves the quality of life and decreases the risk of several diseases (i.e. stroke, hypertension, myocardial infarction, obesity, and malignancies). Skeletal muscles are considered as an endocrine organ that produces myokines characterized by a paracrine or endocrine activity. Irisin is a circulating hormone-like myokine and is secreted as a product of fibronectin type III domain-containing protein 5 from skeletal muscle in response to exercise. This molecule regulates the energy metabolism and acts in adipose tissue, bones, and nervous system. As both animal and clinical studies confirmed the action of irisin in muscle and adipocytes, this protein is considered as adipomyokine. In adipose tissue, irisin stimulates the process of browning of beige precursor fat cells, which are present in white fat cells, and promotes energy expenditure. It affects bone metabolism by increasing osteoblast differentiation and reducing osteoclast maturation. In nervous system, irisin influences hippocampal neurogenesis and neural differentiation of embryonic stem cells in mice and is considered as a messenger between exercise and brain function. However, the existence of this protein and its role in humans is a matter of debate. This study presents irisin as a new champion of the molecule, which could be considered as the messenger in the muscle-fat-bone-brain axis.

Key Words:
Irisin, Adipomyokine, Metabolic, Neurologic influence.

Introduction

With aging, increased tendency toward sarcopenic obesity is observed[1]. Sarcopenia is a medical condition, which is defined by decreased muscle mass and impaired muscle function, which may be associated with frailty. To maintain a proper functioning of muscles, it is important to have an adequate physical activity, which is considered to be as the best nonpharmacological treatment for cardiovascular, metabolic, and bone diseases[2,3]. During exercise, the endocrine activity of muscles releases myokines, which are the crucial molecules in the regulation of energy homeostasis[4,5]. Boström et al[4,6] found that physical activity induces transcriptional regulator peroxisome proliferator-activated receptor-γ co-activator 1α (PGC-1α) in the skeletal muscle. PGC-1α is responsible for the synthesis of fibronectin type III domain-containing protein 5 (FNDC5), which is a membrane protein abundantly expressed in skeletal muscle. Structurally, FNDC5 is a protein that contains a signal peptide and fibronectin type III repeats (Figure 1). The C-terminal tail of FNDC5 is in the cytoplasm, whereas the extracellular N-terminal part is released into the circulation as irisin during proteolytic cleavage[4,6]. The term "irisin" was proposed by Boström et al[4] after Iris, the courier goddess, to underline the function of irisin as a messenger targeting the endocrine signal from skeletal muscle to adipose tissue. In animal models, increased muscle mRNA expression and enhanced irisin plasma concentrations (65%) are observed[4,7]. In humans, irisin circulates at concentrations typical of hormones[8]. It induces the browning process of white adipose tissue (the appearance of "bright" cells in white adipose depots) and increases thermogenesis[9-12]. It influences energy homeostasis, and it is one of the regulators of adipocyte metabolism. However, its function depends on the actual doses of irisin secreted by cells or administered synthetically. Browning of adipose tissue occurs when large amounts of recombinant irisin are administered (3,500 μg kg^{-1}/week); but at lower doses, it modulates the skeletal genes expression (*Opn* and *Sost gene)*[13]. *I*risin also improves the geometry and strength of cortical bone, specifically when trabecular bone

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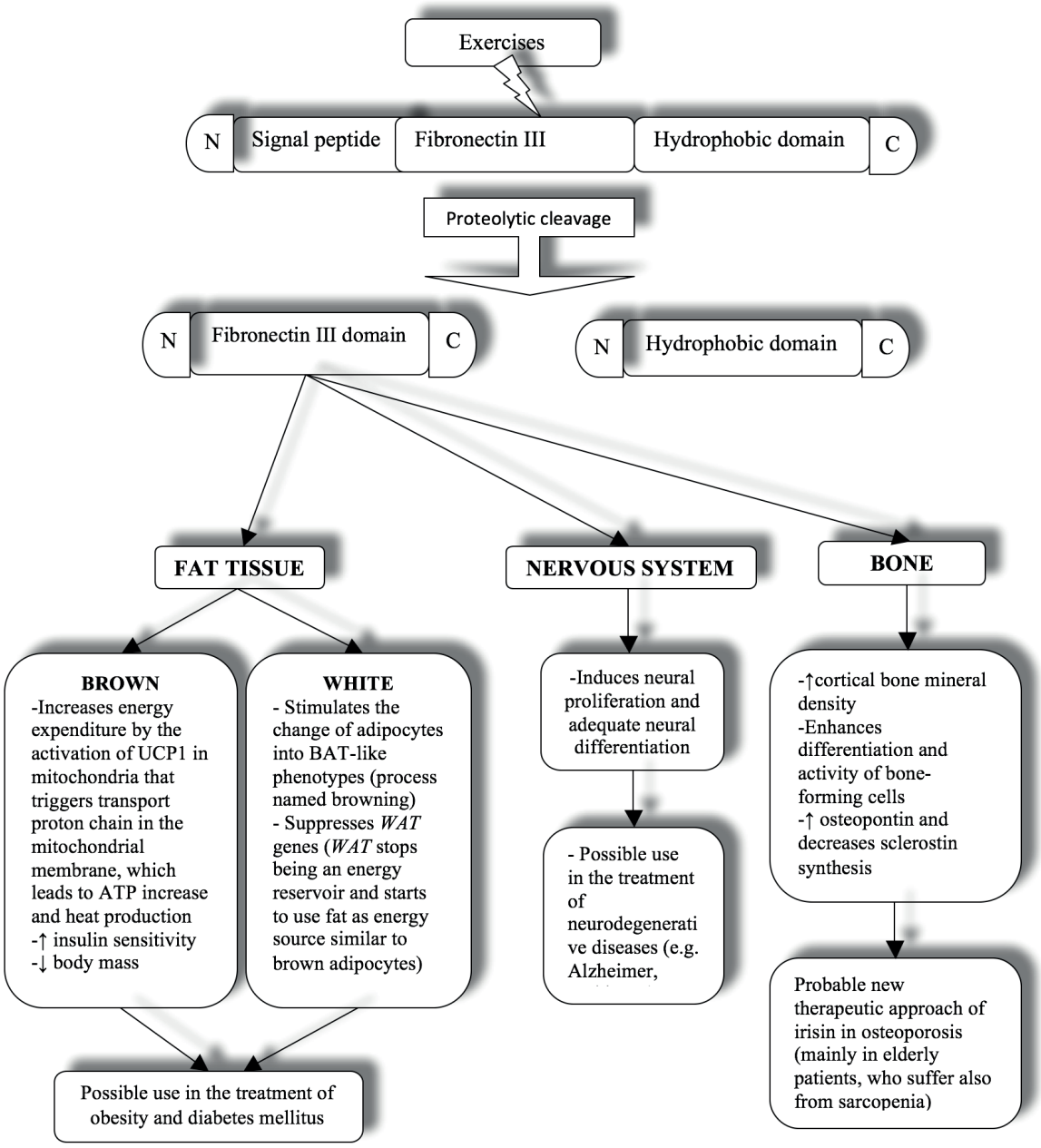

Figure 1. Activation of irisin and its role onthe muscle–fat–bone–brain axis (FNDC5 is proteolytically cleaved and contains an amino (N)-terminal part and a hydrophobic domain inserted in the lipidic bilayer at carboxy (C)-terminal domain).

(which is a calcium reservoir) is spared[14,15]. It is also expressed in brain in low amounts[16,17], and its concentration differs with age (inverse correlation) and gender (higher amounts of irisin were reported in young men compared with middle-aged women)[18]. This study summarizes the most relevant research findings on the role of irisin in muscles, adipose tissue, bones, and brain. As the exact role of irisin in humans is still a matter of debate, we decided to present recent data regarding this interesting molecule and describe its activity in different body parts.

Irisin and Skeletal Muscles

Irisin is a hormone secreted by myocytes and is proposed to be a bridge between exercise and metabolic homeostasis[4,12,18]. The level of irisin positively correlates with the amount of muscle

mass[18,19]. In animals, plasma irisin levels are increased by 65% after 3 weeks of freewheel running, whereas in healthy humans, irisin concentration is doubled after 10 weeks of endurance exercises[4]. An increased level of irisin is also reported in male athletes, 30 minutes after sprinting, but this effect disappears after 8 weeks of training[18]. However, some data did not confirm FNDC5 gene activation by aerobic exercises in younger humans[20], and regular exercises were inversely correlated with irisin concentration in adult men[21]. These discrepancies have been explained by the fact that the level of irisin increases only when more energy is needed, and such condition is observed in sedentary lifestyle, in which ATP concentration is strongly decreased in muscles without physical activity[18].

Irisin and Adipose Tissue

Irisin is not only a myokine but also an adipokine, which serves as a mediator for the beneficial metabolic effects of exercises[4]. In adipose tissue, irisin stimulates the browning of white adipocytes and thermogenesis by the activation of uncoupling protein 1 (UCP1)[4,22]. Brown adipose tissue produces energy through thermogenesis, improving energy homeostasis. Also, irisin inhibits adipogenesis and highlights the potential role of direct signaling from skeletal muscle in brown adipocytes[23]. Not only irisin but also brown fat has a positive influence on the metabolic processes and increases insulin sensitivity and total body energy expenditure, which enables the reduction of body mass[4]. Most of the studies describe the positive correlation between irisin and adiposity [18,24]; however, some researches indicate the negative relation between irisin and the amount of fat tissue[25]. In obese people, elevated irisin level is positively associated with the resting energy expenditure[19]. Decreased concentration of irisin is observed after bariatric surgery[18] or in anorexia nervosa[26], but exercise and lifestyle changes for 1 year, result in the increase of plasma irisin level in obese children[27]. In healthy women, a positive tendency between the circulating irisin and BMI is observed[18,24]; however, this relation disappears after adjusting for the potential confounding factors[18]. Overexpression of irisin causes an increase in glucose tolerance and improvement in insulin sensitivity in high-fat-fed mice[28]. In patients with type 2 diabetes mellitus, serum irisin was found to be negatively associated with hyperglycemia[29], and the level of serum irisin in diabetic patients is lower than that in nondiabetic population[30]. However, some researchers observed an elevated level of irisin in obesity, diabetes mellitus, or metabolic syndrome and suggested the physiological response of this molecule to the improvement of glucose tolerance and lipid profile in patients with these diseases[18,21]. Besides metabolic properties, irisin has a pro-proliferation effect and stimulates the proliferation of endothelial cells of humans[31]. Further studies are needed to elucidate the complexity of irisin interactions with the metabolic endpoints of these facts; however, the role of irisin as a messenger between exercise and metabolic homeostasis may be a reason for the possibility to use it in the therapeutic processes in patients with obesity or diabetes mellitus.

Irisin and Bone Mass

Physical exercise has a beneficial influence on bone metabolism, because cortical bone is highly sensitive to anabolic factors released by muscle[32,33]. In many studies, positive associations between exercise and increased bone size and bone mass are confirmed[32-36]. Higher muscle mass is associated with a higher BMD and reduced risk of fracture in postmenopausal women[37]. Animal and clinical researches have shown some beneficial influence of myokines on bone turnover mediated through myokines[5]. Irisin, released upon physical activity, displays anabolic actions on the skeleton[15]. Indeed, in athletes, irisin level correlates positively with BMD and bone strength[38], but because of decreased physical activity in former athletes, the irisin level leads to a progressive loss of bone[34]. Bone tissue is more sensitive to the irisin action than adipose tissue, and the effect of irisin depends on the administered dose[13]. Recombinant irisin (r-irisin), given at low dose (100 μg kg^{-1}/week**)** in young mice, increases cortical bone mineral density and positively modifies bone geometry, thus pro-osteoblastic genes are upregulated and the activity of osteoblasts increases. Simultaneously, osteoblast inhibitors (e.g. *Spp1* and *Sost* gene) are decreased[13]. These genes are responsible for mechanostimulation[15], and one-month treatment of r-irisin causes increased expression of *Spp1* on cortical surfaces[39,40]. Irisin enhances the level of osteopontin (an osteocyte-specific protein and a component of the bone extracellular matrix), which is a regulator of biomineralization in bone tissue, and decreases the bone formation[41]. Moreover, recombinant irisin injections downregulate sclerostin, a molecule, which decreases the bone formation[42,43]. Similar data are reported in humans, in which plasma irisin level is inversely

correlated with sclerostin concentration independently of age or sex[44]. In addition, circulating irisin is inversely correlated with sclerostin, which not only influences the bone metabolism but also is related to the adiposity and glucose metabolism[44]. Sclerostin plays a role in the formation of bone and fat cell[45]. It increases with aging and is higher in the elderly compared with younger people. The negative association between irisin and sclerostin [44] may be because of the influence of irisin on the stimulation of the browning process of adipocytes[46]. Besides dose-dependent activity, irisin influences the bone metabolism directly[14] or indirectly by brown fat-mediated effects. The direct effects are related to increased osteoblastogenesis (increased differentiation of bone marrow stromal cells into mature osteoblasts)[14] via the Wnt/beta-catenin pathway downstream of the BMP receptor signal and decreased differentiation of osteoclasts[47,48]. Studies *in vivo* showed increased bone trabecular volume, cortical bone mass, geometry, and strength exhibited by irisin in mice[15,47]. Irisin promotes osteogenesis during lineage-specific differentiation[47]. Similar results are reported in humans, in whom irisin levels in young athletes are predicted to increase bone density and strength[38]. Indirect effect of irisin in bones is mediated through the stimulation of adipocyte browning. As mentioned earlier, high doses of recombinant irisin (3,500 μg kg^{-1}/week) affect uncoupling protein 1 (UCP-1) expression in white adipose tissue, whose upregulation causes browning of fat[15]. Brown adipose tissue has a beneficial influence on the skeleton[26, 46, 49] and shows anabolic effect on bones[46]. On the contrary, low dose of irisin does not induce browning of white adipose tissue, and it increases the molecular markers of browning (*UCP1*) or adipogenesis (*PPARγ*)[48]. Moreover, brown adipocyte-synthesized factors may induce osteoblast differentiation in bone marrow, for example, insulin-like growth factor binding protein 2 (IGFBP2)[50]. The association between brown fat and bone strength was proved in women[51], as well as in children and adolescents (increased with cortical thickness)[52]. Moreover, in adult women, lower irisin levels were associated with a higher risk of osteoporotic fractures[53]. Irisin can be used as a atherapeutic molecule in obesity and exercise-associated bone formation[54,55].

The risk of osteoporosis is related to age and gender (the increase of osteoporosis is observed after menopause), which is partially related to hormonal changes. Estradiol level can influence serum sclerostin and irisin synthesis[18,56], and in postmenopausal overweight women with osteoporosis, an inverse correlation between irisin levels and vertebral fragility and fractures is observed[57]. Positive correlations between irisin and estradiol level, muscle mass, and insulin sensitivity are reported[18,25]. On the contrary, older age and increased fat mass, as well as insulin resistance and elevated cholesterol, are negatively correlated with irisin[18,21,25]. Moreover, strong positive correlation between irisin and 24-hour energy expenditure was noted, but only in the group of women with energy expenditure higher than predicted[58]. Recent studies have shown that sclerostin and irisin are partly regulated by estrogen[18,59]. There is also an inverse correlation between serum irisin levels and vertebral fragility or fractures in postmenopausal women[53]. As irisin has beneficial effect in sarcopenia and osteoporosis, new therapeutic approach of this molecule should be considered, particularly in older people, who often suffer from both the diseases.

Irisin and Nervous System

Irisin is also suspected to be the molecular link between muscle and brain. It is expressed in cerebellar Purkinje cells of rats and mice[60] and is necessary for the proper neural differentiation of mice embryonic stem cells[17]. It is suspected that there is a neural pathway participating in the signal transduction of irisin, produced in cerebellum, to adipocytes through intermediary synapses in the medulla and spinal cord[60]. Irisin also influences hippocampal neurogenesis in a dose-dependent manner (high concentrations of irisin 50-100 nmol/L increases the proliferation of neurons)[16]. Because of the positive effect of exercises on neurogenesis and the fact that hippocampus is considered as the main region affected by neurodegenerative diseases (Alzheimer's or Parkinson's disease), irisin is regarded as the molecular messenger between exercise and brain function[61-63]. Data also suggest that some medications can affect the irisin concentration. Recently, statins have been reported to exhibit a crucial influence on both lipid metabolism and irisin concentration[64], and simvastatin has been shown to increase irisin concentration[65]. Beside this, the expression of FNDC5 can also be induced by nutritional factors including polyunsaturated fatty acids (PUFA). The supplementation of omega 3 fatty acids during 24 and 48h has significantly induced irisin expression in human rhabdomyosarcoma cells[66].

Conclusions

Irisin shows a strong relation between skeletal muscle, adipocytes, bone, and neurons, which better explains the comprehensive regulation of skeletal homeostasis exerted by physical exercises. This specific crosstalk between fat, bone, muscle, and neurons shows the significant role of this molecule in the metabolic processes of our body. Utilizing the metabolic and the osteogenic potential of irisin might be a therapeutic choice in treating certain diseases caused by inactive lifestyle. Irisin can play a potential role in pharmacological treatment and can be the representative of a new anabolic therapy in high-burden diseases such as osteopenia/osteoporosis, obesity/sarcopenia, and tumor-associated cachexia. These disorders often occur concurrently and contribute to increased morbidity/mortality and impaired quality of life. Thus, the beneficial role of irisin in many metabolic and osteogenic processes confirms that physical exercise is necessary for the development of an efficient load-bearing skeleton, browning process in white adipose tissue, and proper function of neurons. Many studies underline the positive role of irisin in metabolic processes; however, the therapeutic potential of this molecule is temporarily questioned. The animal studies have shown an undeniable thermogenic effect of irisin; but in humans, this effect remains controversial. Additional studies with the larger sample size are needed to systematically identify these interacting links and their causal relations. Also, regular exercises are crucial for everyday health and quality of life.

Conflict of interest

The authors declare no conflicts of interest.

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