Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4814 - 4829
Received 25 April 2021; Accepted 08 May 2021.

A Review on Physiological Role of IRISIN: In Vitro and in Vivo Studies

Dr. P.Adi lakshmi[1], Dr. V.Suganthi[2]
[1]Asst. professor, Nimra institute of medical sciences, Jupudi, Vijayawada, Andhrapradesh.
[2]Prof&HOD Physiology Department VMKV medical college and hospital,Salem, Tamilnadu.
email: [1]dr.adilakshmiperla@gmail.com, [2]vsuganthiarasan@gmail.com2

ABSTRACT

Prevalence and mortality rate due to non-communicable diseases has been increasing over a past decade. Sedentary life style or physical inactivity is considered as a high risk factor for development of about 35 types of chronic diseases and reduced life expectancy. Scientific evidence shows that regular exercise has beneficial effects on disease prevention, management of pre symptomatic disease and to stop further progression of disease. Until the discovery of irisin in 2012, the beneficial effects of exercise was attributed to peroxisome proliferator activated receptor γ(PPARγ). Bostrom et al reported that exercise upregulates the expression of a transcription factor peroxisome proliferator activated receptor γ coactivator 1-α (PGC1- α) in skeletal muscles. PGC1- α cleaves fibronectin type III domain containing 5(FNDC 5) and releases irisin into circulation. Since then research is going on to know the beneficial effects of irisin. Few studies explained the effects of irisin on glucose homeostasis, insulin resistance, hypertension, fight against obesity, bone mineral density and immunity. Few scientists raised doubts regarding the existence of irsin and its role in metabolism and beneficial effects. In this review, we summarised the controversies regarding synthesis, release, effect of various types of exercise on irisin levels and physiological actions of Irisin.

Keywords:
Irisin, PGC1- α, FNDC5, myokine GLUT-4 ,exercise, metabolism

1.Introduction

Several diseases can be prevented, treated or reversed by implementing certain life style changes, which include regular physical exercise and consuming healthy diet. Many studies highlight the promising benefits of exercise on health . But the exact mechanism of beneficial effects is unclear; until the discovery of IRISIN by Bostrom et.al. Contracting skeletal muscles secrete many myokines which have autocrine, paracrine and endocrine effects. These myokines include myostatin, IL-6, IL-10, IL-15, TNF-α, Brain derived factor, myonectin, decorin, irisin, osteonectin. (1, 2) Among all these Irisin has gained much attention due to its beneficial effects.

KEY ROLE OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR –γ (PPAR-γ) COACTIVATOR -1α (PGC- 1 α):

PGC 1 α, a transcriptional co-activator is expressed in several tissues such as skeletal muscle, brown adipose tissue, heart, brain and kidney. PGC-1α gene is located on chromosome number 4 in humans(3). PGC-1α binds to PPAR-γ to stimulate the transcription of genes. Originally, PGC-1α is induced by cold environment and mediates its action by stimulating sympathetic nervous system (4). PGC-1α secretion can also be stimulated by acute as well as chronic exercise (5-8). The induced PGC-1α exerts beneficial effects like fibre type conversion, increases fatty acid oxidation, mitochondrial biogenesis and angiogenesis(3, 9). Furthermore, PGC-1α activates thermo genesis by stimulating genes involved in brown fat development, like UCP1 (10, 11). In conjunction with these genes, five more muscle proteins: Interleukin-15, Fndc5(Fibronectin type III domain containing protein 5), VEGF β (Vascular endothelial growth factor β), Lrg1 (Leucine–rich alpha-2- glycoprotein 1) and TIMP 4 (Tissue inhibitor of Metalloproteinases-4) are encoded by PGC 1α. The expression of IL-15, Fndc5, VEGF β, TIMP 4 genes were also observed in muscle biopsies following endurance exercise in humans (12, 13).Previous studies did not

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4814 - 4829
Received 25 April 2021; Accepted 08 May 2021.

describe the role of Fndc5. In 2012 Bostrom et.al. investigated the role of Fndc5 following exercise.

Fndc5 also known as FRCP2 (Fibronectin type III repeat containing protein 2) is synthesised as a type 1 trans membrane protein with 209 amino acids in humans (14,15). It consists of an N-terminal 29 amino acid signal sequence, a fibronectin III domain, a transmembrane domain and a 39 residue cytoplasmic segment. when commercially available FNDC5 was used in cultured white adipose tissue, Fndc5 up regulated Un coupling protein 1 (UCP1) mRNA 7-500 fold at a concentration of 20nM and other brown fat genes Elovl 3(Elongation of very long chain fatty acids protein 3), COX 7a (Cytochrome C oxidase subunit 7a) and Otop 1(Otopetrin proton channel 1) and down regulated leptin genes. The cells treated with Fndc5 showed raise in mitochondrial gene expression, proliferation of mitochondria and 100% increase in total oxygen consumption. (16.). This thermogenic action of FNDC5 is mediated through increasing the levels of PPAR α. Previous studies could not investigate further actions of Fndc5 and in 2012 Bostrom et. al. extended their study and discovered that Fndc5 cleaved to form irisin(16).

2. Secretion of Irisin:

Fndc5 is processed, cleaved at C terminus and secreted as soluble Irisin. This 112 amino acid polypeptide secreted from muscles communicates with other tissues; so it was named Irisin, after the Greek messenger goddess "Iris". Bostrom et.al. detected the existence of irisin by administration of intravenous adeno viral delivery of full length FNDC5 into wild type mice. They used western blot technique to study the presence of irisin and detected an immune reactive band at 22 kDa. They also measured the blood concentration of irisin after exercise in both mice and humans. Mice showed significant increase in Irisin concentration (65%) after 3 weeks of free wheel running, where as human beings showed a two fold increase in Irisin after 10 weeks of endurance training. They concluded that Irisin is present both in mice and humans with 100% structural identity between them (16). In contrast to the findings of Bostrom et al., Raschke S. et al. found difference in the sequence between humans and most rodents and primates. The ATG codon in other species is mutated to ATA codon in humans. Raschke S. et al. flung doubts regarding Fndc5 mRNA expression in muscle biopsies after endurance and strength training in healthy men. They reported that neither endurance nor resistance training elevated Fndc5 mRNA This may be due to a different type of antibody used by Raschke S. et al. (17). Later, extensive research was conducted to prove the existence of irisin in humans, to explain the influence of various types of exercise on its secretion and its role in health and disease states. In this review, the controversies regarding physiological role of irisin and the type of exercise that stimulates irisin secretion is discussed.

3. Exercise and Irisin:

Till now more than 100 studies investigated the effect of different types of exercises on irisin levels. These studies analysed Fndc5, PGC1 α, and irisin levels in blood and m RNA levels in various tissues like skeletal muscle and adipose tissues. For the first time Bostrom et al. explained the capacity of exercise to alter the metabolism through irisin (16). After this, Raschke S. et al. reported conflicting results that neither endurance nor strength training could activate FNDC5 gene and subsequent irisin formation (17). Since then many in vitro and in vivo studies were conducted to study the response of various types of exercise. A wide variety of exercise protocols /techniques, intensities, duration and frequencies were employed on humans , C2C12

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4814 - 4829
Received 25 April 2021; Accepted 08 May 2021.

myotubes, C57 BL / 6J mice and wistar rats. Animal studies also reported conflicting results. In some studies irisin rise was parallel with FNDC5 and PGC-1 α and few studies could not confirm the simultaneous increase in FNDC5 and PGC-1 α with irisin(18,19). The irisin rise was observed in animals fed with high fat diet and serum irisin showed negative correlation with insulin resistance, cholesterol , triglyceride levels and fat mass (20,21).

The first human study was conducted by Norheim F et al. They examined FNDC5 expression in skeletal muscles, plasma irisin levels and subcutaneous adipose tissue browning after long term exercise training. They observed increase in FNDC5 and PGC-1 α expression in muscle but could not detect increase in irisin levels and its effect on browning of subcutaneous white adipose tissue (22). The response to endurance exercise is dependent on the intensity, maximal O2 consumption, (VO2 max) and duration of exercise. Endurance exercise protocols of > 45 min, moderate to high intensity protocols, >65% VO_2 max increased irisin levels in blood and saliva. But Vo2 max <65% failed to alter irisin levels (23,24,25,26). One study compared endurance and interval exercise with resistance exercise and concluded that strength type of exercise was more effective(27).Two studies implemented interval type of exercise protocol with positive results(28,29). One meta analysis study evaluated the effects of chronic exercise training. The study included 3 randomised and nine non-randomised trials. This study revealed no response to resistance exercise training and in fact there was decrease in irisin levels following exercise (30). In fact the studies detected low irisin levels in athletes and physically active individuals compared to sedentary individuals(25,31,32,33). Results of strength exercise training demonstrated that it may not alter either FNDC5 gene or the irisin concentration (17, 34-36,37,38). In contrast to it, Kim HJ et al., Kim H et al., Reisi J et al. had reported a 20% - fivefold increase in irisin concentration after strength training exercise(39,40). Reisi J et al. studied the effect of strength training on irisin, FNDC5 gene and UCP1 gene in abdominal subcutaneous WAT of Sprague Dawley male rats and reported a positive correlation with exercise(41).

The diversity of the results among humans and animal studies can be attributed to interspecies variation of irisin structure, total training load, the methodologies employed to detect irisin. Most of the studies measured irisin by ELISA assays. The available ELISA kits have some cross reactivity with other proteins in serum / plasma proteins(42). Due to this irisin levels varied from thousands to <1ng/ml in healthy or unhealthy subjects. To some extent the controversies were resolved by mass spectrometry. Lee et al. and Jedrychowski et al. measured irisin using mass spectrometry. They detected a 12 kDa protein band after removal of albumin and deglycosylation of plasma samples(43, 44). Western blot technique also identified protein bands between 12kDa to 35kDa range (45). In inactive males the concentration of irisin is ~ 3.6ng/ml and exercise training may increase the level to 4.3ng/ml (44). Further research on human beings is needed to evaluate the type and intensity of exercise that influence irisin secretion.

4. Irisn Effect on Browning And Adipogenesis:

In humans, brown adipose tissue (BAT) is present in the cervical, supra clavicular, axillary, paravertebral and peri renal regions (46, 47). The BAT thermogenic effect is mediated through UCP1. UCP1 inhibits ATP synthesis by transporting protons across the inner mitochondrial membrane. This uncouples the electron transport chain from energy production to heat production and dissipates energy as heat (43, 48). It has been proposed that factors like irisin, PGC1-α released during exercise drive browning of adipose tissue(16). Fndc5 stimulates thermogenic programme in cervical adipocytes and to a lesser degree in subcutaneous adipocytes(44). Recombinant murine irisin has the ability to induce UCP1 in human adipose

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4814 - 4829
Received 25 April 2021; Accepted 08 May 2021.

derived stem cells and in 3T3L1 fibroblasts during adipogenesis (49,50). Yuan Zhang et al. observed the up regulation of UCP1 protein in both cultured primary mature white adipocytes, fresh human sub coetaneous white adipose tissues and preadipocytes by irisin. The effect of Irisin was studied in peri renal fat adipocytes. The human perirenal fat express high UCP1 levels independent of irisin levels. Beige adipocytes in scWAT are more sensitive to irisin than brown adipose tissue from perirenal fat. The expression of UCP1 is mediated through extracellular signal-related kinase(ERK) and p38 mitogen activated protein kinase (p38 MAPK) signalling. The lowest dose for up regulation of UCP1 levels is 5nmol/l and three-fold increase was observed at 50nmol/l concentration of irisin. The duration of exposure to increase UCP1 levels is as early as two days . More over irisin can stimulate PGC1α and NRF (Nuclear respiratory factor) 1&2. The browning effect of irisin was compared with two familiar browning agonists, rosiglitazone (PPARG ligand agonist) and CL-316243 (β_3- adrenergic receptor agonist) in scWAT. They induced UCP1, PGC1α, and NRF at concentrations of 50nmol/l, 1μmol/l, 1μmol/l respectively. They also found that when irisin was added during stem cell adipogenic differentiation, it stimulated osteoblastic differentiation and inhibited adipogenesis(51). There are controversies about browning effect of irisin. Raschke et al. could not find browning of primary human subcutaneous preadipocytes after 18 days of irisin treatment(17). However, Lee et al. and Huh et al. found browning effect by irisin in human mature adipocytes after 6 days and 8 days respectively (43, 50). The conflicting results can be due to the variation in the maturity of adipocytes. Irisin could promote browning effect in mature adipocytes, with no effect on stem cell adipocytes. Irisin treated adipocytes are smaller and accumulate less amount of lipids than control adipocytes(51). Irisin inhibits maturation of adipocytes, adipogenic differentiation genes and BAT related genes in adipocyte stem cells. This may be the reason for the conflicting results. Irisin treated, mature human adipocytes showed browning genes like UCP1, PR domain containing 16(PRDM 16) and Cell death inducing DNA fragmentation factor like effector A(CIDEA). Irisin inhibited basal lipolysis and the lipids were utilised for browning effect. The acetoacetyl co-A, intermediate products of tricarboxylic acid cycle, glucose metabolism and protein metabolism were altered in irisin treated adipocytes. Thus Irisin regulates energy homeostasis through transcription, translation and altering metabolism(50). If there are consistent positive results from experiments on human beings, in future it would become the therapeutic tool for metabolic disorders.

5. Metabolic effects of irisin on skeletal muscle:

Irisin secreted from skeletal muscle in response to both exercise and exposure to cold, act in an autocrine fashion to mediate its effects (16). The first work was done by Vaughan et al. by using murine myocytes (C2C12).In vitro studies on C_2C_{12} myocytes demonstrated that irisin had different effects on skeletal muscle in a time and dose dependent manner. It increased basal oxygen consumption after 24 hours at 2.5nM, 5nM, 10nM of concentration. There was marked increase in mitochondrial content, functioning and decrease in mitochondrial uncoupling. These results indicated that irisin can increase the cellular oxidative metabolism. On further investigation it was observed that irisin has the ability to increase the expression of genes like PGC-1α, glucose transporter 4 (GLUT4), NRF-1(Nuclear respiratory factor-1), mitochodrial transcription factor A (TFAM) & mitochondrial uncoupling protein 3 (UCP3). Irisin treated cells initially depend on glycolysis till the mitochondrial functioning reaches optimum level to meet energy demands (52). Irisin acts as a promyogenic factor and induces skeletal muscle growth. A large number of genes involved in skeletal muscle growth were analysed by microarray analysis

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4814 - 4829
Received 25 April 2021; Accepted 08 May 2021.

and the results were confirmed by subsequent q PCR (quantitative real time polymerase chain reaction) technique. Irisin curtailed negative regulators of myogenic differentiation factors like SRY related HMG-box (sox 8) and heyL. It stimulated Cxcl1, pentraxin-3, skeletal muscle hypertrophy promoting factors haptoglobin and interleukin6. On further investigation it was noted that irisin increased number of myotubes, myoblast fusion index, fusion markers: myomaker, caveolin-3. The proteins that control myogenesis include Myo D, p21, myogenin and myosin heavy chain (MHC). However irisin significantly increased only p21 and MHC expression, which suggested that recombinant irisin can enhance myogenesis in mouse and human myotubes. Histological studies done to analyse the irisin effect on muscle hypertrophy revealed distinct increase in muscle hypertrophy. The signalling pathways activated during skeletal muscle hypertrophy are ERK1/2, Akt, mTOR. Furthermore it was found that irisin attenuated denervation induced muscle atrophy by stimulating satellite cells activation and their proliferation(40-50). Interleukin -6 (IL-6), one of the exercise induced myokine also regulates skeletal muscle hypertrophy via myoblast differentiation, proliferation and satellite cell activation. Irisin up regulates Il-6 and promotes satellite proliferation (53-57). JY Huh et.al investigated expression of irisin/FNDC5 levels in human skeletal muscle cells during myogenic differentiation . The concentration of Fndc5 peaked at day 5 and attained a plateau from day 8. Irisin levels increased only after day 8. By gene expression analysis they reported increase in IGF1, PGC1α and decrease in myostatin levels (50). Further research on human skeletal muscle is needed to extend the promising effects of recombinant irisin in skeletal muscle disorders.

6. Role of irisin in Glucose Homeostasis:

Several hormones regulate blood glucose homeostasis directly or indirectly by modulating glucose uptake, glycolysis, glycogen synthesis, gluconeogensis, glycogenolysis(58) In this review, all the disparities between in vivo and in vitro studies were discussed. Irisin regulates blood glucose levels directly and indirectly. Irisin exerts direct effects by altering glucose uptake and metabolism in adipose tissue, skeletal muscle and liver.

Irisin released from skeletal muscle induces browning of white adipose tissue via p38 mitogen-activated protein kinase (MAPK) and ERK pathways (59,60) and subsequent increase in glucose uptake occurs in the newly formed brown adipose tissue. The glucose uptake of brown adipose tissue is insulin dependent and 10 times more than WAT and visceral adipose tissue.(61) This glucose uptake is a consequence of up regulation of GLUT4 (glucose transporter -4) expression in human mature adipocytes. Moreover, irisin stimulates glycolysis which is evidenced by increased secretion of lactate from human mature adipocytes of subcutaneous adipose tissue (62).

Irisin in a dose and time dependent manner acts on skeletal muscle. When skeletal muscles are treated with irisin, significant increase in uptake of glucose and fatty acid was observed. Irisin mediated these effects by up regulating genes involved in glucose transport (GLUT4, Hexokinase2). It down regulates genes involved in glycogenolysis gluconeogenesis (phosphoenolpyruvate carboxykinase1) (63). Irisin stimulates glucose uptake via activating AMPK pathway, which translocates GLUT4 to plasmamembrane of skeletal muscle cells. The AMPK pathway is induced through reactive oxygen species (ROS) and this in turn led to activation of p38 MAPK pathway (64). Irisin treated mice primary hepatocytes and hepatocytes derived from human hepato cellular carcinoma decreased gluconeogenesis via PI3K-AKT-FOXO1 pathway . This pathway down regulates the enzymes of gluconeogenesis: PCK 1 and G6PC(65). Irisin stimulates glycogen synthesis by activating PI3K-AKT- glycogen synthase kinase 3 pathway. In mouse hepatic cells irisin reduced lipogenesis and lipid accumulation cells

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4814 - 4829
Received 25 April 2021; Accepted 08 May 2021.

also(66). Further, irisin lowered cholesterol content in hepatic cells by preventing sterol regulatory element-binding protein 2(50). In liver FNDC5 was expressed via constitutive androstane receptor (CAR) (67). Through these signalling pathways irisin maintain euglycemic levels.

The indirect effects of irisin is mediated through activation of PGC1 ALPHA-IRISIN-BETATROPHIN AXIS (68). However more clarification is required to elucidate the association between irisin and other hormones and the major contribution of irisin in glucose homeostasis.

7. Irisin Action on Beta Cells of Pancreas:

Both Type 1 and Type 2 diabetes can be treated in a better way by triggering beta cell proliferation by inhibiting apoptosis of beta cells, replacing or regenerating the beta cells of pancreas (68). In 2013 Yi P et.al, identified a hormone betatrophin, also known as Angiopoietin-like protein8(ANGPTL8). It is mainly secreted from liver and adipose tissue in mice. They found that betatrophin promotes proliferation of beta cells in pancreas and glucose tolerance in mice. This opened a new door for regenerative β-cell therapy in humans(69). The exercise hormone Irisin was also reported to have beneficial effects in diabetics. Irisin stimulates p38MAPK and ERK pathways during adipogenesis (59). The pathway p38 MAPK coordinates cellular responses to stress stimuli, mediates oxidative stress-sensitive cell signalling pathways. Researches assumed that rise in ROS (reactive oxygen species) and irisin may stimulate p38 MAPK-PGC1-ALPA -BETATROPHIN pathway which results in beta cell regeneration(66). Few studies raised paradoxical statements that there is no association between either betatrophin or irisin on pancreatic beta cell proliferation function and insulin resistance(70, 71). More research is essential to explain the associations of betatrophin and irisin on beta cell activity and proliferation.

8. Irisin role on bone physiology:

Irisin from skeletal muscle, communicates with bone and regulates bone remodelling by its action on osteoblasts, osteocytes and osteoclasts. It stimulates cortical bone mass and bone strength but the trabecular bone is spared from irisin action. It stimulates new bone synthesis by up regulating the pro–osteoblastic genes in osteoblasts and inhibits osteoclastic process. Irisin derived from mice myoblasts triggers osteoblast differentiation. It promotes osteogenesis by up regulating Runx 2 (Runt –related transcription factor) , Atf4 (marrow activating transcription factor4) gene expression, alkaline phosphatase and collagen type I, alpha 1(col1a1) mRNA(72,73). It down regulates sclerostin secretion from osteocytes. Sclerostin is a product of the SOST gene and is an inhibitor of Wnt/ β catenin signalling pathway (74). Wnt/ β catenin pathway is the key regulator of osteoblast differentiation and bone formation. Therefore decrease in sclerostin levels were associated with increased osteogenesis. In vitro studies give additional evidence that irisin stimulates Wnt pathway by up regulating Lrp5 and β-catenin genes. Under the influence of irisin bone mineral density, bone strength, periosteal circumference and calcium deposition were increased via phosphorylation of P38 and ERK (75). The primary osteoblast differentiation and osteogenic activity of irisin was observed at a 35 fold lower dose than required for browning. All these effects resembled the beneficial effects of exercise (72). Irisin also stimulated osteogenic differentiation genes osteocalcin and osteopontin (76) Yaxian Ma et al. studied irisin effect on mouse macrophage cell line RAW264.7 cells and bone marrow monocytes. They reported that Irisin proliferates osteoclast precursors but inhibits their

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4814 - 4829
Received 25 April 2021; Accepted 08 May 2021.

differentiation. It inhibits osteoclastogenesis by suppressing the expression of osteoclstogenesis-related genes. R-irisin treated cells showed reduced mRNA of RANK, NFATc1, cathepsin K, and TRAP. These effects were confirmed by measuring the protein levels of cathepsin K and TRAP in cultured cells. The signalling pathways that play a pivotal role in osteoclast proliferation in irisin treated cells are p38 and JNK pathways. Irisin inhibits osteoclast differentiation via down regulation of RANKL induced NF-Kb pathway (77). The results were supported by another recent study. Eden G Estell et al. demonstrated that irisin regulates bone remodelling not only by osteoblastic stimulation but also by promoting differentiation and proliferation of osteoclasts. They claimed that the discrepancy in the results can be due to variation in the dose R Irisin and duration of exposure of bone cells. Irisin regulates bone remodelling by binding toα5/ β5 integrins present on osteocytes (78). All these studies gave a hope that, in future recombinant irisin may be recommended to prevent and treat osteoporosis.

9. Irisin and blood pressure:

Exercise is considered as a non–pharmacological therapy and exercise can lower blood pressure even in persons who are not responsive to medical treatment (79). Different studies proposed varying theories about the mechanism by which exercise decreases blood pressure. The mechanisms proved to be effective include such as decrease in sympathetic stimulation, rennin-angiotensin-aldosterone axis, enhanced baroreceptor activity, and vascular endothelial nitric acid synthase activity(80-82). One recent study explained the modulating effect of exercise on heart, arteries and skeletal muscle in reducing blood pressure. Zhang et al. studied the effect of irisin by injecting into 3rd ventricle of male Sprague- Dawley rats. Within few minutes of irisin administration, a sustained rise in cardiac output and blood pressure was observed. These effects were mediated by activation of paraventricular nucleus of hypothalamus. This proved that irisin stimulate central nervous system to coordinate the cardiovascular functions. However opposite effects were observed on peripheral administration of irisin. Reduction in both systolic as well as diastolic blood pressure without any change in cardiac contractility was reported after intravenous injection of recombinant human irisin into rats. This suggested that the peripheral effects of irisin may be due to its effects on smooth muscle cells and endothelial cells and not due to the alteration in the cardiac output. They also explained that R- irisn induced vessel dilation through K_{ATP} channels activation in vessel rings with or without endothelium(83).

Jinjuan et al. also observed the similar effects of irisin on blood pressure. They noticed a dose dependent effect of irisin on blood pressure in rats. The reduction in blood pressure started 5 minutes after intravenous injection of 10 ug/kg of irisin, significant increase after 10minutes, and maximum effect was noted after 20minutes. After 90 minutes the effect was no longer. Irisin did not affect heart rate, vasodilation in mesenteric arteries from rats but augmented Ach- mediated vasorelaxation and decreased PHE(phenylephrine) induced vasoconstriction of mesenteric arteries from rats. These effects of irisin were caused by activation of endothelial nitric oxide synthase and subsequent increase in nitric oxide release by endothelial cells via activation of AMPK and Akt pathways (84). Further research is needed to enlighten these results in humans too.

10. Irisin and Nervous system:

Another well known fact about exercise is, it improves brain health and cognitive function (85-87) Exercise induces neurotrophins, most importantly brain derived neurotropic factor (BDNF) in

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4814 - 4829
Received 25 April 2021; Accepted 08 May 2021.

hippocampus(85). BDNF stimulate brain development, increases neuronal cell differentiation, migration, dendritic branching, synaptogenesis, plasticity, learning and memory (88,89). FNDC5/Irisin presence is detected in purkinje cells of cerebellum, human cerebrospinal fluid, paraventricular neurons of hypothalamus. Exercise induced expression of FNDC5 resulted in up regulation of BDNF genes, and also genes involved in hippocampal functioning which include Npas4 (Neural PAS domain), cFos, and Arc(Activity- regulated cytoskeleton- associated protein). BDNF released boosts reward related learning and motivation. In vivo studies reported that FNDC5 levels increase during differentiation of human embryonic stem cell derived neural cells into neurons. During brain development forced fndc5 expression enhanced the survival and maturation of primary cortical neurons (90). Further research is required to understand the irisin effects and mechanism of action on human brain.

11. Anti inflammatory effects of irisin:

Cells produce a wide variety of cytokines. These intracellular signalling molecules regulate inflammation and immune response in an autocrine and paracrine fashion. Irisin plays important role in inflammation. Macrophages cultured in irisin rich medium showed decrease in overproduction of reactive oxygen species (91) A study conducted by Mazur Bialy demonstrated the influence of irisin on pro inflammatory activity of adipocytes and mechanism of action in the regulation of pro inflammatory cytokines. They analysed that pre treatment of high irisin concentration down regulated TLR4/ MyD88 (Myeloid differentiation primary response protein) pathway in macrophages activated with lipopolysaccharide. It also inhibited the phosphorylation of downstream proteins such as MAP kinases, Janus kinses, ERK(Extracellular signal – regulated kinase). Furthermore, it also decreased the mRNA expression of TNF-α (Tumor necrosis factor alpha), IL-B, IL-6, MCP-1(Monocyte chemoattractant protein -1), KC (keratinocyte chemoattractant), HMGB1(high mobility group box 1). (92)

12. Conclusion:

Irisin can be the future remedy for metabolic disorders since it improves weight loss by regulating glucose and fat metabolism. It regulates bone turnover, promotes beta cell functioning, influences brain activity, protects heart and vascular system. It acts as anti-inflammatory, anti-oxidant and anti-aging agent. However, the underlying mechanisms, receptors through which irisin regulates all the functions still remains unclear and require further investigation.
Conflict of interests: Declare no conflicts of interest.

References

[1] Pedersen, B. K., & Febbraio, M. A. (2008). Muscle as an endocrine organ: focus on muscle-derived interleukin-6.

[2] Physiological reviews, 88(4), 1379–1406.

[3] Pedersen, B. K., Akerström, T. C., Nielsen, A. R., & Fischer, C. P. (2007). Role of myokines in exercise and metabolism. Journal of applied physiology (Bethesda, M. : 1985), 103(3), 1093–1098.

[4] Puigserver, P., & Spiegelman, B. M. (2003). Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator. Endocrine reviews, 24(1), 78–90.

[5] Puigserver, P., Wu, Z., Park, C. W., Graves, R., Wright, M., & Spiegelman, B. M. (1998). A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell, 92(6), 829–839.

[6] Baar, K., Wende, A. R., Jones, T. E., Marison, M., Nolte, L. A., Chen, M., Kelly, D. P., & Holloszy, J. O. (2002). Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 16(14), 1879–1886.

[7] Goto, M., Terada, S., Kato, M., Katoh, M., Yokozeki, T., Tabata, I., & Shimokawa, T. (2000). cDNA Cloning and mRNA analysis of PGC-1 in epitrochlearis muscle in swimming-exercised rats. Biochemical and biophysical research communications, 274(2), 350–354.

[8] Norrbom, J., Sundberg, C. J., Ameln, H., Kraus, W. E., Jansson, E., & Gustafsson, T. (2004). PGC-1alpha mRNA expression is influenced by metabolic perturbation in exercising human skeletal muscle. Journal of applied physiology (Bethesda, Md. : 1985), 96(1), 189–194.

[9] Russell, A. P., Feilchenfeldt, J., Schreiber, S., Praz, M., Crettenand, A., Gobelet, C., Meier, C. A., Bell, D. R., Kralli, A., Giacobino, J. P., & Dériaz, O. (2003). Endurance training in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-gamma coactivator-1 and peroxisome proliferator-activated receptor-alpha in skeletal muscle. Diabetes, 52(12), 2874–2881.

[10] van Raalte, D. H., Li, M., Pritchard, P. H., & Wasan, K. M. (2004). Peroxisome proliferator-activated receptor (PPAR)-alpha: a pharmacological target with a promising future. Pharmaceutical research, 21(9), 1531–1538.

[11] Barbera, M. J., Schluter, A., Pedraza, N., Iglesias, R., Villarroya, F., & Giralt, M. (2001). Peroxisome proliferator-activated receptor alpha activates transcription of the brown fat uncoupling protein-1 gene. A link between regulation of the thermogenic and lipid oxidation pathways in the brown fat cell. The Journal of biological chemistry, 276(2), 1486–1493.

[12] Sears, I. B., MacGinnitie, M. A., Kovacs, L. G., & Graves, R. A. (1996). Differentiation-dependent expression of the brown adipocyte uncoupling protein gene: regulation by peroxisome proliferator-activated receptor gamma. Molecular and cellular biology, 16(7), 3410–3419.

[13] Vind, B. F., Pehmøller, C., Treebak, J. T., Birk, J. B., Hey-Mogensen, M., Beck-Nielsen, H., Zierath, J. R., Wojtaszewski, J. F., & Højlund, K. (2011). Impaired insulin-induced site-specific phosphorylation of TBC1 domain family, member 4 (TBC1D4) in skeletal muscle of type 2 diabetes patients is restored by endurance exercise-training. Diabetologia, 54(1), 157–167.

[14] Nielsen, A. R., & Pedersen, B. K. (2007). The biological roles of exercise-induced cytokines: IL-6, IL-8, and IL-15. Applied physiology, nutrition, and metabolism =

Physiologie appliquee, nutrition et metabolisme, 32(5), 833–839.

[15] Teufel, A., Malik, N., Mukhopadhyay, M., & Westphal, H. (2002). Frcp1 and Frcp2, two novel fibronectin type III repeat containing genes. Gene, 297(1-2), 79–83.

[16] Ferrer-Martínez, A., Ruiz-Lozano, P., & Chien, K. R. (2002). Mouse PeP: a novel peroxisomal protein linked to myoblast differentiation and development. Developmental dynamics : an official publication of the American Association of Anatomists, 224(2), 154–167.

[17] Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., Rasbach, K. A., Boström, E. A., Choi, J. H., Long, J. Z., Kajimura, S., Zingaretti, M. C., Vind, B. F., Tu, H., Cinti, S., Højlund, K., Gygi, S. P., & Spiegelman, B. M. (2012). A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature, 481(7382), 463–468.

[18] Raschke,S., and Eckel,J. (2013 Jun). "Adipo-myokines: two sides of the same coin—mediators of inflammation and mediators of exercise". Mediators of Inflammation, vol. 2013,320724.

[19] Fain, J. N., Company, J. M., Booth, F. W., Laughlin, M. H., Padilla, J., Jenkins, N. T., Bahouth, S. W., & Sacks, H. S. (2013). Exercise training does not increase muscle FNDC5 protein or mRNA expression in pigs. Metabolism: clinical and experimental, 62(10), 1503–1511.

[20] Tiano, J. P., Springer, D. A., & Rane, S. G. (2015). SMAD3 negatively regulates serum irisin and skeletal muscle FNDC5 and peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) during exercise. The Journal of biological chemistry, 290(12), 7671–7684.

[21] Lu, Y., Li, H., Shen, S. W., Shen, Z. H., Xu, M., Yang, C. J., Li, F., Feng, Y. B., Yun, J. T., Wang, L., & Qi, H. J. (2016). Swimming exercise increases serum irisin level and reduces body fat mass in high-fat-diet fed Wistar rats. Lipids in health and disease, 15, 93.

[22] Mazur-Bialy, A. I., Bilski, J., Wojcik, D., Brzozowski, B., Surmiak, M., Hubalewska-Mazgaj, M., Chmura, A., Magierowski, M., Magierowska, K., Mach, T., & Brzozowski, T. (2017). Beneficial Effect of Voluntary Exercise on Experimental Colitis in Mice Fed a High-Fat Diet: The Role of Irisin, Adiponectin and Proinflammatory Biomarkers. Nutrients, 9(4), 410.

[23] Norheim, F., Langleite, T. M., Hjorth, M., Holen, T., Kielland, A., Stadheim, H. K., Gulseth, H. L., Birkeland, K. I., Jensen, J., & Drevon, C. A. (2014). The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. The FEBS journal, 281(3), 739–749.

[24] Pekkala, S., Wiklund, P. K., Hulmi, J. J., Ahtiainen, J. P., Horttanainen, M., Pöllänen, E., Mäkelä, K. A., Kainulainen, H., Häkkinen, K., Nyman, K., Alén, M., Herzig, K. H., & Cheng, S. (2013). Are skeletal muscle FNDC5 gene expression and irisin release regulated by exercise and related to health?. The Journal of physiology, 591(21), 5393–5400. https://doi.org/10.1113/jphysiol.2013.263707

[25] Tsuchiya, Y., Ando, D., Takamatsu, K., & Goto, K. (2015). Resistance exercise

induces a greater irisin response than endurance exercise. Metabolism: clinical and experimental, 64(9), 1042–1050.

[26] Huh, J. Y., Mougios, V., Kabasakalis, A., Fatouros, I., Siopi, A., Douroudos, I. I., Filippaios, A., Panagiotou, G., Park, K. H., & Mantzoros, C. S. (2014). Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation. The Journal of clinical endocrinology and metabolism, 99(11), E2154–E2161.

[27] Tsuchiya, Y., Ando, D., Goto, K., Kiuchi, M., Yamakita, M., & Koyama, K. (2014). High-intensity exercise causes greater irisin response compared with low-intensity exercise under similar energy consumption. The Tohoku journal of experimental medicine, 233(2), 135–140.

[28] Huh, J. Y., Siopi, A., Mougios, V., Park, K. H., & Mantzoros, C. S. (2015). Irisin in response to exercise in humans with and without metabolic syndrome. The Journal of clinical endocrinology and metabolism, 100(3), E453–E457.

[29] Winn, N. C., Grunewald, Z. I., Liu, Y., Heden, T. D., Nyhoff, L. M., & Kanaley, J. A. (2017). Plasma Irisin Modestly Increases during Moderate and High-Intensity Afternoon Exercise in Obese Females. PloS one, 12(1), e0170690

[30] Briken, S., Rosenkranz, S. C., Keminer, O., Patra, S., Ketels, G., Heesen, C., Hellweg, R., Pless, O., Schulz, K. H., & Gold, S. M. (2016). Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. Journal of neuroimmunology, 299, 53–58.

[31] Qiu, S., Cai, X., Sun, Z., Schumann, U., Zügel, M., & Steinacker, J. M. (2015). Chronic Exercise Training and Circulating Irisin in Adults: A Meta-Analysis. Sports medicine (Auckland, N.Z.), 45(11), 1577–1588.

[32] Pardo, M., Crujeiras, A. B., Amil, M., Aguera, Z., Jiménez-Murcia, S., Baños, R., Botella, C., de la Torre, R., Estivill, X., Fagundo, A. B., Fernández-Real, J. M., Fernández-García, J. C., Fruhbeck, G., Gómez-Ambrosi, J., Rodríguez, R., Tinahones, F. J., Fernández-Aranda, F., & Casanueva, F. F. (2014). Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. International journal of endocrinology, 2014, 857270.

[33] Hew-Butler, T., Landis-Piwowar, K., Byrd, G., Seimer, M., Seigneurie, N., Byrd, B., & Muzik, O. (2015). Plasma irisin in runners and nonrunners: no favorable metabolic associations in humans. Physiological reports, 3(1), e12262.

[34] Kerstholt, N., Ewert, R., Nauck, M., Spielhagen, T., Bollmann, T., Stubbe, B., Felix, S. B., Wallaschofski, H., Gläser, S., & Friedrich, N. (2015). Association of circulating irisin and cardiopulmonary exercise capacity in healthy volunteers: results of the Study of Health in Pomerania. BMC pulmonary medicine, 15, 41.

[35] Hecksteden, A., Wegmann, M., Steffen, A., Kraushaar, J., Morsch, A., Ruppenthal, S., Kaestner, L., & Meyer, T. (2013). Irisin and exercise training in humans - results from a randomized controlled training trial. BMC medicine, 11, 235.

[36] Bang, H. S., Seo, D. Y., Chung, Y. M., Oh, K. M., Park, J. J., Arturo, F., Jeong, S. H., Kim, N., & Han, J. (2014). Ursolic Acid-induced elevation of serum irisin augments

muscle strength during resistance training in men. The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology, 18(5), 441–446.

[37] Ellefsen, S., Vikmoen, O., Slettaløkken, G., Whist, J. E., Nygaard, H., Hollan, I., Rauk, I., Vegge, G., Strand, T. A., Raastad, T., & Rønnestad, B. R. (2014). Irisin and FNDC5: effects of 12-week strength training, and relations to muscle phenotype and body mass composition in untrained women. European journal of applied physiology, 114(9), 1875–1888..

[38] Scharhag-Rosenberger, F., Meyer, T., Wegmann, M., Ruppenthal, S., Kaestner, L., Morsch, A., & Hecksteden, A. (2014). Irisin does not mediate resistance training-induced alterations in resting metabolic rate. Medicine and science in sports and exercise, 46(9), 1736–1743

[39] Boeselt, T., Nell, C., Lütteken, L., Kehr, K., Koepke, J., Apelt, S., Veith, M., Beutel, B., Spielmanns, M., Greulich, T., Vogelmeier, C. F., Kenn, K., Janciauskiene, S., Alter, P., & Koczulla, A. R. (2017). Benefits of High-Intensity Exercise Training to Patients with Chronic Obstructive Pulmonary Disease: A Controlled Study. Respiration; international review of thoracic diseases, 93(5), 301–310.

[40] Kim, H. J., So, B., Choi, M., Kang, D., & Song, W. (2015). Resistance exercise training increases the expression of irisin concomitant with improvement of muscle function in aging mice and humans. Experimental gerontology, 70, 11–17.

[41] Kim, H. J., Lee, H. J., So, B., Son, J. S., Yoon, D., & Song, W. (2016). 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. Physiological research, 65(2), 271–279.

[42] Reisi, J., Ghaedi, K., Rajabi, H., & Marandi, S. M. (2016). Can Resistance Exercise Alter Irisin Levels and Expression Profiles of FNDC5 and UCP1 in Rats?. Asian journal of sports medicine, 7(4), e35205

[43] Albrecht, E., Norheim, F., Thiede, B., Holen, T., Ohashi, T., Schering, L., Lee, S., Brenmoehl, J., Thomas, S., Drevon, C. A., Erickson, H. P., & Maak, S. (2015). Irisin - a myth rather than an exercise-inducible myokine. Scientific reports, 5, 8889.

[44] Lee, P., Linderman, J. D., Smith, S., Brychta, R. J., Wang, J., Idelson, C., Perron, R. M., Werner, C. D., Phan, G. Q., Kammula, U. S., Kebebew, E., Pacak, K., Chen, K. Y., & Celi, F. S. (2014). Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. Cell metabolism, 19(2), 302–309.

[45] Jedrychowski, M. P., Wrann, C. D., Paulo, J. A., Gerber, K. K., Szpyt, J., Robinson, M. M., Nair, K. S., Gygi, S. P., & Spiegelman, B. M. (2015). Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. Cell metabolism, 22(4), 734–740.

[46] Perakakis, N., Triantafyllou, G. A., Fernández-Real, J. M., Huh, J. Y., Park, K. H., Seufert, J., & Mantzoros, C. S. (2017). Physiology and role of irisin in glucose homeostasis. Nature reviews. Endocrinology, 13(6), 324–337.

[47] Sidossis, L., & Kajimura, S. (2015). Brown and beige fat in humans: thermogenic

adipocytes that control energy and glucose homeostasis. The Journal of clinical investigation, 125(2), 478–486.

[48] Svensson, P. A., Lindberg, K., Hoffmann, J. M., Taube, M., Pereira, M. J., Mohsen-Kanson, T., Hafner, A. L., Rizell, M., Palming, J., Dani, C., & Svensson, M. K. (2014). Characterization of brown adipose tissue in the human perirenal depot. Obesity (Silver Spring, Md.), 22(8), 1830–1837.

[49] Cannon, B., & Nedergaard, J. (2004). Brown adipose tissue: function and physiological significance. Physiological reviews, 84(1), 277–359.

[50] Reza, M.M., Subramaniyam, N., Sim, C.M., Ge, X., Sathiakumar, D., Mcfarlane, C., Sharma, M., & Kambadur, R. (2017). Irisin is a pro-myogenic factor that induces skeletal muscle hypertrophy and rescues denervation-induced atrophy. Nature Communications, 8.

[51] Huh, J. Y., Dincer, F., Mesfum, E., & Mantzoros, C. S. (2014). Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans. International journal of obesity (2005), 38(12), 1538–1544.

[52] Zhang, Y., Xie, C., Wang, H., Foss, R. M., Clare, M., George, E. V., Li, S., Katz, A., Cheng, H., Ding, Y., Tang, D., Reeves, W. H., & Yang, L. J. (2016). Irisin exerts dual effects on browning and adipogenesis of human white adipocytes. American journal of physiology. Endocrinology and metabolism, 311(2), E530–E541.

[53] Vaughan, R. A., Gannon, N. P., Barberena, M. A., Garcia-Smith, R., Bisoffi, M., Mermier, C. M., Conn, C. A., & Trujillo, K. A. (2014). Characterization of the metabolic effects of irisin on skeletal muscle in vitro. Diabetes, obesity & metabolism, 16(8), 711–718.

[54] Baeza-Raja, B., & Muñoz-Cánoves, P. (2004). p38 MAPK-induced nuclear factor-kappaB activity is required for skeletal muscle differentiation: role of interleukin-6. Molecular biology of the cell, 15(4), 2013–2026.

[55] Austin, L., & Burgess, A. W. (1991). Stimulation of myoblast proliferation in culture by leukaemia inhibitory factor and other cytokines. Journal of the neurological sciences, 101(2), 193–197.

[56] Cantini, M., Massimino, M. L., Rapizzi, E., Rossini, K., Catani, C., Dalla Libera, L., & Carraro, U. (1995). Human satellite cell proliferation in vitro is regulated by autocrine secretion of IL-6 stimulated by a soluble factor(s) released by activated monocytes. Biochemical and biophysical research communications, 216(1), 49–53.

[57] Okazaki, S., Kawai, H., Arii, Y., Yamaguchi, H., & Saito, S. (1996). Effects of calcitonin gene-related peptide and interleukin 6 on myoblast differentiation. Cell proliferation, 29(4), 173–182.

[58] Serrano, A. L., Baeza-Raja, B., Perdiguero, E., Jardí, M., & Muñoz-Cánoves, P. (2008). Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. Cell metabolism, 7(1), 33–44.

[59] Gerich J. E. (2000). Physiology of glucose homeostasis. Diabetes, obesity & metabolism, 2(6), 345–350.

[60] Zhang, Y., Li, R., Meng, Y., Li, S., Donelan, W., Zhao, Y., Qi, L., Zhang, M., Wang, X., Cui, T., Yang, L. J., & Tang, D. (2014). Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes, 63(2), 514–525.

[61] Orava, J., Nuutila, P., Lidell, M. E., Oikonen, V., Noponen, T., Viljanen, T., Scheinin, M., Taittonen, M., Niemi, T., Enerbäck, S., & Virtanen, K. A. (2011). Different metabolic responses of human brown adipose tissue to activation by cold and insulin. Cell metabolism, 14(2), 272–279.

[62] Huh, J. Y., Mougios, V., Skraparlis, A., Kabasakalis, A., & Mantzoros, C. S. (2014). Irisin in response to acute and chronic whole-body vibration exercise in humans. Metabolism: clinical and experimental, 63(7), 918–921.

[63] Lee, H. J., Lee, J. O., Kim, N., Kim, J. K., Kim, H. I., Lee, Y. W., Kim, S. J., Choi, J. I., Oh, Y., Kim, J. H., Suyeon-Hwang, Park, S. H., & Kim, H. S. (2015). Irisin, a Novel Myokine, Regulates Glucose Uptake in Skeletal Muscle Cells via AMPK. Molecular endocrinology (Baltimore, Md.), 29(6), 873–881.

[64] 64. Liu, T. Y., Shi, C. X., Gao, R., Sun, H. J., Xiong, X. Q., Ding, L., Chen, Q., Li, Y. H., Wang, J. J., Kang, Y. M., & Zhu, G. Q. (2015). Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes. Clinical science (London, England : 1979), 129(10), 839–850.

[65]

[66] Park, M. J., Kim, D. I., Choi, J. H., Heo, Y. R., & Park, S. H. (2015). New role of irisin in hepatocytes: The protective effect of hepatic steatosis in vitro. Cellular signalling, 27(9), 1831–1839.

[67] Tang, H., Yu, R., Liu, S., Huwatibieke, B., Li, Z., & Zhang, W. (2016). Irisin Inhibits Hepatic Cholesterol Synthesis via AMPK-SREBP2 Signaling. EBioMedicine, 6, 139–148. https://doi.org/10.1016/j.ebiom.2016.02.

[68] Mo, L., Shen, J., Liu, Q., Zhang, Y., Kuang, J., Pu, S., Cheng, S., Zou, M., Jiang, W., Jiang, C., Qu, A., & He, J. (2016). Irisin Is Regulated by CAR in Liver and Is a Mediator of Hepatic Glucose and Lipid Metabolism. Molecular endocrinology (Baltimore, Md.), 30(5), 533–542.

[69] Sanchis-Gomar, F., & Perez-Quilis, C. (2014). The p38-PGC-1α-irisin-betatrophin axis: Exploring new pathways in insulin resistance. Adipocyte, 3(1), 67–68.

[70] Crunkhorn S. (2013). Metabolic disorders: Betatrophin boosts β-cells. Nature reviews. Drug discovery, 12(7), 504.

[71] Yi, P., Park, J. S., & Melton, D. A. (2013). Betatrophin: a hormone that controls pancreatic β cell proliferation. Cell, 153(4), 747–758.

[72] Lingshu Wang, Jun Song, Chuan Wang, Peng Lin,Kai Liang, Yu Sun, Tianyi He, Wenjuan Li, Ruxing Zhao, Jun Qin,Yiran Lu, Jinbo Liu et al. (2016). Circulating Levels of Betatrophin and Irisin Are Not Associated with Pancreatic β -Cell Function in Previously Diagnosed Type 2 Diabetes Mellitus Patients. J Diabetes Res, 2016,

2616539

[73] Gusarova, V., Alexa, C. A., Na, E., Stevis, P. E., Xin, Y., Bonner-Weir, S., Cohen, J. C., Hobbs, H. H., Murphy, A. J., Yancopoulos, G. D., & Gromada, J. (2014). ANGPTL8/betatrophin does not control pancreatic beta cell expansion. Cell, 159(3), 691–696.

[74] 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, J. E., Colucci, S., New, M. I., Zaidi, M., Cinti, S., & Grano, M. (2015). The myokine irisin increases cortical bone mass. Proceedings of the National Academy of Sciences of the United States of America, 112(39), 12157–12162.

[75] Colaianni, G., Cuscito, C., Mongelli, T., Oranger, A., Mori, G., Brunetti, G., Colucci, S., Cinti, S., & Grano, M. (2014). Irisin enhances osteoblast differentiation in vitro. International journal of endocrinology, 2014, 902186.

[76] Delgado-Calle, J., Sato, A. Y., & Bellido, T. (2017). Role and mechanism of action of sclerostin in bone. Bone, 96, 29–37.

[77] Zhang, J., Valverde, P., Zhu, X. et al. (2017)Exercise-induced irisin in bone and systemic irisin administration reveal new regulatory mechanisms of bone metabolism. Bone Res 5, 16056 (2017).

[78] Qiao, X., Nie, Y., Ma, Y., Chen, Y., Cheng, R., Yin, W., Hu, Y., Xu, W., & Xu, L. (2016). Corrigendum: Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways. Scientific reports, 6, 21053. h

[79] Ma, Y., Qiao, X., Zeng, R., Cheng, R., Zhang, J., Luo, Y., Nie, Y., Hu, Y., Yang, Z., Zhang, J., Liu, L., Xu, W., Xu, C. C., & Xu, L. (2018). Irisin promotes proliferation but inhibits differentiation in osteoclast precursor cells. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, fj201700983RR.

[80] Kim, H., Wrann, C. D., Jedrychowski, M., Vidoni, S., Kitase, Y., Nagano, K., Zhou, C., Chou, J., Parkman, V. A., Novick, S. J., Strutzenberg, T. S., Pascal, B. D., Le, P. T., Brooks, D. J., Roche, A. M., Gerber, K. K., Mattheis, L., Chen, W., Tu, H., Bouxsein, M. L., … Spiegelman, B. M. (2018). Irisin Mediates Effects on Bone and Fat via αV Integrin Receptors. Cell, 175(7), 1756–1768.

[81] Dimeo, F., Pagonas, N., Seibert, F., Arndt, R., Zidek, W., & Westhoff, T. H. (2012). Aerobic exercise reduces blood pressure in resistant hypertension. Hypertension, 60(3), 653–658.

[82] Gu, Q., Wang, B., Zhang, X. F., Ma, Y. P., Liu, J. D., & Wang, X. Z. (2014). Contribution of renin-angiotensin system to exercise-induced attenuation of aortic remodeling and improvement of endothelial function in spontaneously hypertensive rats. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology, 23(5), 298–305.

[83] Matsukawa, K., Ishii, K., Kadowaki, A., Liang, N., & Ishida, T. (2012). Differential effect of central command on aortic and carotid sinus baroreceptor-heart rate reflexes at the onset of spontaneous, fictive motor activity. American journal of physiology.

Heart and circulatory physiology, 303(4), H464–H474.

[84] Sun, M. W., Zhong, M. F., Gu, J., Qian, F. L., Gu, J. Z., & Chen, H. (2008). Effects of different levels of exercise volume on endothelium-dependent vasodilation: roles of nitric oxide synthase and heme oxygenase. Hypertension research : official journal of the Japanese Society of Hypertension, 31(4), 805–816.

[85] Zhang, W., Chang, L., Zhang, C., Zhang, R., Li, Z., Chai, B., Li, J., Chen, E., & Mulholland, M. (2015). Central and peripheral irisin differentially regulate blood pressure. Cardiovascular drugs and therapy, 29(2), 121–127.

[86] Fu, J., Han, Y., Wang, J., Liu, Y., Zheng, S., Zhou, L., Jose, P. A., & Zeng, C. (2016). Irisin Lowers Blood Pressure by Improvement of Endothelial Dysfunction via AMPK-Akt-eNOS-NO Pathway in the Spontaneously Hypertensive Rat. Journal of the American Heart Association, 5(11), e003433.

[87] Cotman, C. W., Berchtold, N. C., & Christie, L. A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends in neurosciences, 30(9), 464–472.

[88] Mattson M. P. (2012). Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell metabolism, 16(6), 706–722.

[89] Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. Trends in cognitive sciences, 17(10), 525–544.

[90] Greenberg, M. E., Xu, B., Lu, B., & Hempstead, B. L. (2009). New insights in the biology of BDNF synthesis and release: implications in CNS function. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29(41), 12764–12767.

[91] Park, H., & Poo, M. M. (2013). Neurotrophin regulation of neural circuit development and function. Nature reviews. Neuroscience, 14(1), 7–23.

[92] Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J. D., Greenberg, M. E., & Spiegelman, B. M. (2013). Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell metabolism, 18(5), 649–659.

[93] Mazur-Bialy A. I. (2017). Irisin acts as a regulator of macrophages host defense. Life sciences, 176, 21–25.

[94] Mazur-Bialy, A. I., Pocheć, E., & Zarawski, M. (2017). Anti-Inflammatory Properties of Irisin, Mediator of Physical Activity, Are Connected with TLR4/MyD88 Signaling Pathway Activation. International journal of molecular sciences, 18(4), 701..