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STRUCTURE, MECHANISM, AND ROLE OF IRISIN IN CERTAIN PATHOLOGICAL DISORDERS

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Abstract: In addition to being the primary storage site for glycogen, muscles release many myokines, mainly cytokines and chemokines that regulate growth, metabolism, and inflammatory responses such as IL-6, MCP-1, adiponectin, and irisin. Irisin is a novel myokine that is mainly expressed in muscles and adipose tissues, as well as the liver, heart, brain, thyroid, stomach, testes, cerebrospinal fluid, and other organs. It is a glycoprotein composed of 112 A.A residues with a molecular weight about 12 to 15 kD. Irisin production is stimulated through exercise, cold, dietary, and hormonal effects, where the expression of FNDC5 mRNA in the skeleton has been shown to increase after exercise. The AMPK-PGC-1-FNDC5 path is considered to be the main path of hormone synthesis through proteolysis of the FNDC5 molecule, which contains 209 residues of amino acids by the metalopeptidase enzyme family, where the irisin out-membrane part of FNDC5. There are currently no specific receptors for irisin, but it does its role by interacting with integrins, especially those integrin's αV. This research aims to highlight the working mechanism of irisin and its role in many disorders as a potential therapeutic target for many neurological, bone, and metabolic disorders.

Keywords: Irisin; Myokine; FNDC5; Obesity; Alzheimer.

INTRODUCTION

The major location of glycogen synthesis for glucose storage is thought to be muscle. It has also lately gained recognition as a secretory organ that can release different myokines. [1] Myocytes secrete myokines, primarily chemokines and cytokines, which regulate growth, angiogenesis, and metabolism through endocrine, paracrine, and autocrine signaling, according to unique patterns of change in myokines gene expression in the muscle and serum levels immediately following the start of exercise [2]. This implies that myocytes release myokines, mostly chemokines and cytokines, which control growth, angiogenesis, and metabolism via autocrine, paracrine, and endocrine signaling. Interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), monocyte chemotactic protein 1 (MCP1), and myostatin are the principal myokines. [3-5] Myokines can have some beneficial biological effects, such as anti-inflammatory actions in both acute and chronic low-grade inflammation [6] causing the interaction between myokines and other cytokines and controlling systemic inflammatory response. [7]

A transmembrane protein fibronectin type III domain-containing protein 5 (FNDC5), which was found and demonstrated to be expressed in a variety of tissues and organs including skeletal muscle, adipose tissue,

liver, bones, brain, heart, and pancreas, was first identified in 2002. [8] In 2012, Boström et al. demonstrated that the extracellular component of FNDC5 protein was released into the blood circulation as a response to exercise in mice. [9] This secretory soluble peptide was created as a result of proteolytic processing of FNDC5 protein,[10] and that molecule induced changes in adipose tissue and activated thermogenesis.[9] Additionally, the recently discovered protein known as "irisin" was suggested to connect muscles and other bodily tissues.[11]

Irisin is a myokine that is mainly expressed in skeletal muscle, as well as the liver, pancreas, sweat glands, subcutaneous, and adipose tissues.[12] Smaller quantities of iris are also generated by the testes, brain, spleen, heart, and stomach, according to immunohistochemical investigations. Irisin has also been observed in the cerebellum, thyroid, pineal gland, cerebrospinal fluid, and human fetuses.[13,14] Irisin is released from muscles after they contract, allowing it to interact with both bone and adipose tissue.[15] Molecular weight measurements between 10 and 32 kDa have been reported in a number of investigations.[16] Irisin has a wide range of physiological effects, including increased nitric oxide production, vasodilation, and improvements in white fat tissue conversion to brown fat tissue, systemic metabolism, insulin resistance, and glucose tolerance.[17,18]

In order to treat polycystic ovarian syndrome, Prader-Willi syndrome, hypothyroidism, and other metabolic and endocrine disorders, it may be used to affect adipose tissue and glycemic homeostasis. Irisin could be an effective treatment option for conditions brought on by a sedentary lifestyle because of its osteogenic capacity. [14]

Irisin reduces inflammation in adipose tissue and inhibits the expression and release of pro-inflammatory cytokines in the obese individuals.[19] Irisin also contributes to carcinogenesis, albeit its influence on the development of cancer is unclear at the moment.[20] In comparison to controls, patients with renal cell carcinoma had greater serum irisin levels.[21] The majority of investigations have found that cancer has increased irisin expression.[22] Other studies observed, however, that irisin expression decreased in cancer patients.[20] In vitro, r-irisin reduced epithelial-to-mesenchymal transition (EMT) in pancreatic cancer (PC), epithelial ovarian cancer (EOC), lung cancer (LC), cell growth, migration, and invasion by upregulating AMP-activated protein kinase (AMPKa) phosphorylation, [25] and inhibiting PI3K/Akt- and STAT3-mediated signaling.[26] Irisin suppresses cell proliferation and causes cancerous cancer cells to stop dividing.[27] Irisin inhibits MCF-7 and MDA-MB-231 breast cancer malignant cell line's capacity to proliferate, migrate, and survive by promoting caspase activity and triggering apoptosis, according to research conducted in vitro.[28] These findings suggest that irisin has an anticancer effect on tumor tissues.[29]

Structure and manufacturing of irisin

Irisin, a hormone with a glycoprotein structure and 112 amino acids, is produced by the proteolysis of the (FNDC5) molecule.[9,3] Rats and people share a perfect structural similarity for the irisin hormone. [17] Irisin is a piece of the fibronectin type III domain-containing protein 5 (FNDC5), a cell membrane protein.[9]

The FNDC5 protein has 209 amino acid residues in total. It composed of an N-terminal signal sequence peptide with 29 A.A (for endoplasmic reticulum targeting nascent FNDC5), which is followed by a putative fibronectin-III (FN-III) domain (the major extracellular portion of irisin) with 94 A.A, an unknown region with 28 A.A (a connecting peptide), a transmembrane domain with 19 A.A (a hydrophobic transmembrane domain), and a 39 A.A C-terminal portion (cytoplasmic carboxy-terminal domain) (Figure 1). Irisin is created by proteolytic cleavage of the extracellular N-terminal region [22,30-31].

Because irisin up-regulation was seen after strength training and high-intensity exercise but not after endurance exercise, it is hypothesized that the kind of physical activity affects the control of irisin levels

[32,33]. The rise of irisin concentration is also facilitated by whole-body vibration exercise [34]. Diet, hormonal control, and cold exposure are other factors that alter irisin levels.[35, 36] The liberation of irisin into blood circulation is strongly influenced by the pathological circumstances linked to various disorders.[37] It has been documented that impaired glucose/lipid metabolism in non-diabetic obese persons leads to an increase in irisin production.[38]

Although skeletal muscle and adipose tissue are the primary sources of irisin, it has also been found to be generated in tissues such as heart tissue, cerebral arteries, kidneys, tongue, and the rectum.[13] Irisin can be released from the perirenal adipose tissue (PRAT), which immediately surrounds the kidney and is strongly linked to renal tissue.[23] Adipose tissue in humans expresses FNDC5 mRNA at a level that is around 100 times lower than that of skeletal muscle [39]. Over the past few years, as our understanding has grown, it has become clear that muscle is a significant target organ for irisin.[40] Irisin's paracrine, autocrine, and endocrine functions allow us to think of it as a hormone.[41]

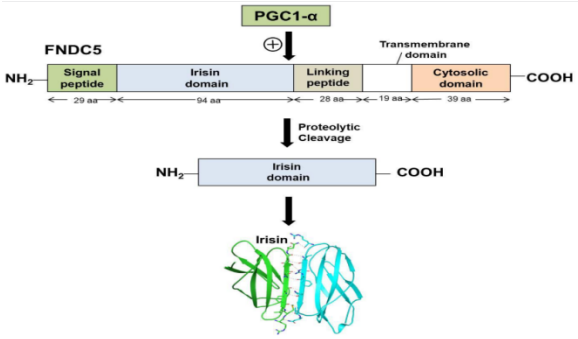
Increased FNDC5 mRNA has been seen after exercise in the skeleton of humans and mice. [42], Peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), a transcription cofactor that is active in the skeletal muscles and controls the transcription of the FNDC5 protein found in the membrane of myocytes, is a crucial element in the control of energy metabolism. PGC-1α increases the expression of FNDC5 to produce more membrane-bound FNDC5. [43,44] The amount of PGC-1α rises along with an increase in mitochondrial biogenesis. [45]

The most crucial route for irisin production is AMPK-PGC-1α-FNDC5. With each contraction of the skeletal muscles during exercise, the amount of Ca^{+2} ions in the muscle cytoplasm rises significantly. This increases the phosphorylation of AMPK, [46] which then increases PGC-1α and controls the transcription of subsequent proteins like FNDC5. Myostatin KO in skeletal muscle significantly boosted PGC-1α and FNDC5/irisin expression, according to Shan et al. [47] Ge et al. discovered that myostatin increased miR-34a to decrease the production of FNDC5/irisin. [48]

Irisin is a FNDC5 out-membrane element.[22] While FNDC5's N-terminal gets released into circulation upon proteolytic cleavage as irisin, FNDC5's C-terminal is found in the cytoplasm. After the N-terminal signal peptide is eliminated, the polypeptide is proteolytically cleaved from the C-terminal moiety, glycosylated, and released as a hormone [3, 9, 49]. One of the most typical post-translational modifications of proteins that take place in the Golgi apparatus and the lumen of the endoplasmic reticulum is glycosylation. There is a lot of variety in the glycan structures as a result of the multi-stage, enzyme-controlled attachment of carbohydrates. Proteins' physicochemical characteristics are modified by oligosaccharides, which are also crucial for achieving the correct conformation of proteins, protecting them from proteolysis, and serving biological purposes in many metabolic processes.[50] Three possible N-glycosylation sites can be identified in the FNDC5 sequence, two of them(Asn36 and Asn81) are already occupied by N-glycans (oligosaccharides). The stability of the molecule is significantly impacted by the lack of oligosaccharides. De-N-glycosylated FNDC5 is not integrated into cell membrane and is unable to adopt a typical spatial shape. As a result, the amount of irisin secreted into the blood is significantly reduced.[51,52] Depending on amount and structure of oligosaccharides linked to the protein molecule, FNDC5 mass varies from 20 to 32 kDa.[9,2] Additionally, irisin possesses two N-glycosylation sites at the locations of Asn-7 and Asn-52. Irisin is released into the bloodstream after becoming N-glycosylated at the two possible sites (Asn7 and Asn52) in ER and being broken down by ADAM-10 and other members of the dis-integrin and metallopeptidase domain family of proteins. [51,53,54] Irisin's molecular weight is reduced by deglycosylation to 12 kDa [55] or 15 kDa. [53] The crystal structure of irisin includes a flexible C-terminal tail (residues 124 to 140) and an N-terminal domain that resembles fibronectin 3 (FNIII).[56]

Studies using X-ray crystallography and biochemical methods revealed that irisin forms as homodimers, in which sheets are formed between the units. Along with hydrogen bonds, interactions between neighboring

subunit side chains, particularly those between Arg-75 and Glu-79, help to maintain this structure and safeguard ends of the dimer and Trp90/Trp90.[3]



(Figure1) Structure of FNDC5 and irisin formation [57].

Mechanism of irisin action

Irisin-specific receptors have not yet been identified. [19] Recent research has demonstrated that irisin binds to integrins, namely αV integrin receptors, in order to act in certain tissues.[58] Transmembrane receptors called integrins are widely expressed and bind extracellular matrix ligands, soluble ligands, and membrane proteins from other cells (cell-matrix interactions).[59] Cell adhesion, migration, and aggregation are all controlled by them.[60] Irisin primarily affects signaling pathways for mitogen-activated protein kinase (MAPK), according to recent research. In addition to these routes, irisin also works in the signal transducer and activator of transcription 3 (STAT3)/Snail, phosphatidylinositol 3-kinase/protein kinase B, and 5′ adenosine monophosphate-activated protein kinase (AMPK) pathways. [61]

Adipocytes, lipid-containing cells that make up adipose tissue, are fat cells.[62] Lipoblasts produce adipocytes. White fat tissue (WFT) and brown fat tissue (BFT), two separate fatty tissues with distinct functions and morphologies, are generated from lipoblasts in mammals.[63] PRAT, in contrast to traditional visceral fat, consists of both white and brown adipose tissues.[64] Under some circumstances, PRAT can also be changed into BAT.[55]

By storing extra energy as triglycerides, WAT produces adipokines that control a range of biological processes, including inflammatory responses.[65-67] The greatest endocrine tissue in humans may be represented by WFT. Leptin, ghrelin, adiponectin, glucocorticoids, plasminogen activator inhibitor (PAI-1), TNF-α, IL-6, and irisin are a few of the adipocytokines released by WFT.[63]

BFT is crucial to maintaining body temperature since it is skilled at producing heat (thermogenesis). Due to its abundance of tiny lipid droplets, centrally placed nucleus, and many mitochondria, BAT differs morphologically from WAT. The main functions of the lipids found in BAT include oxidative phosphorylation and heat production. The mitochondrial membrane of BAT expresses uncoupling protein 1 (UCP-1), also known as thermogenin, which is essential to these activities [67, 68, 69].

Irisin stimulates the peroxisome proliferator-activated receptor (PPARα) which increases white adipose tissue cells' expression of the mitochondrial UCP1 pump, which helps to promote the phenotypic switch from white to brown adipocytes.[70] Inhibiting ATP synthesis and increasing heat generation, raised UCP1 expression.[17] As a result, the cell uses more energy and drives the metabolism of lipids and glucose, which boosts the oxidation of free fatty acids (FFAs) [45,71,72].[70]

By reducing the production of UCP1, the irisin gene is suppressed, which promotes the formation of adipogenesis.[73] Furthermore, it activates the cAMP-protein kinase A (PKA)-hormone-sensitive lipase (HSL)/perilipin pathway, which causes lipolysis.[74]

PRAT accumulation might increase FFA release, which causes lipotoxicity and increases renal damage. The major causes of the development of OB-CKD include adipose tissue accumulation, such as PRAT (lipotoxicity), activation of several inflammatory markers, and elevated oxidative stress. Irisin might lessen renal damage in HFD mice and lower the albumin-to-creatinine ratio. These results were correlated with the browning of PRAT and the recovery of the glomerular VEGF-NO axis activity. [75–23] Low irisin levels may be a risk factor for CKD as they are frequently lower in CKD patients. [76,77] Irisin can help reduce kidney damage brought on by sepsis.[78]

Irisin's role in metabolic disorders

The group of metabolic disorders known as MetS include hyperglycemia, hypertension, hyperlipidemia, and abdominal obesity. These problems are all associated with obesity and raise the risk of cardiovascular disease. [79] A new hormone called irisin offers a potential therapy for metabolic diseases.[14] Because it enhances hepatic glucose and lipid metabolism and increases glucose absorption into skeletal muscle, the irisin molecule works as an insulin sensitizer.[74] Irisin is regarded as a significant therapy option for diabetes since it improves insulin sensitivity, enhances glycogenesis, and inhibits gluconeogenesis.[19] Additionally, irisin stimulates skeletal muscle absorption of glucose through AMPK-related pathways, indicating irisin's beneficial effects on glucose metabolism. As a result, it is predicted that irisin may affect diabetes in the future. Irisin also aids in the development of beta cells [74] and encourages the maintenance of beta cell activities in the pancreas by lowering endoplasmic reticulum stress.[73] According to some theories, elevated irisin levels are caused by problems with insulin sensitivity, lipid and glucose metabolism, and this raises the possibility of an interaction between irisin and adiponectin that leads to increased energy expenditure in adipocytes.[6] By increasing myocyte and adipocyte mitochondrial density and metabolic rate, irisin plays a significant roles in treating metabolic disorders.[80] Irisin controls thermogenesis and prevents adipogenesis in adipose tissue, acting as a mediator for the favorable metabolic benefits of exercise.[72] The energy substrates for the organism start to be high amounts of triglycerides as a result of irisin's ability to increase energy expenditure.[71]

Irisin significantly decreases adipose tissue's synthesis and release of pro-inflammatory cytokines while increasing the release of anti-inflammatory cytokines including TNF-α and IL-6.[73,81] Therefore, chronic inflammation brought on by obesity is reduced by raising anti-inflammatory cytokine levels.[82] Irisin also inhibits leptin's production and release, an adipokine linked to pro-inflammatory activation, and upregulates levels of the anti-inflammatory cytokine adiponectin. It also reduces the expression of monocyte chemoattractant protein-1 (MCP-1) and leptin.[81] The development of metabolic syndrome and insulin resistance are intimately related to leptin activity.[83] The expression of FNDC5 in adipose tissue is influenced by leptin.[84] Insulin sensitivity is increased by the anti-inflammatory adipokine adiponectin, whose quantity is observed to be reduced in obese individuals and might be related to the appearance of insulin resistance. [85] Exercise-induced irisin competitively inhibits the binding of myeloid differentiation factor 2 (MD2) and Toll-like receptor 4 by creating a complex with MD 2 in hepatocytes, and thereby inhibits the inflammatory response. This inhibition of the inflammatory response may help to improve NAFLD via decreasing fibrosis and steatosis in the liver. [86] While ghrelin, leptin , and irisin are produced to regulate the distribution of fat in primary thyroid insufficiency, an elevated TSH level causes adipogenesis. The TSH levels have therefore revealed that irisin levels are elevated in hypothyroidism. [87,88].

Irisin activates the AMPK-PEPCK/G6Pase pathway to inhibit gluconeogenesis, according to studies have demonstrated that it reduces the expression of glucose-6-phosphatase-mediated gluconeogenesis and phosphoenolpyruvate carboxykinase in the liver. Reducing AMPK small interfering RNA (AMPK siRNA) can counteract this effect[89]; It has also been found that irisin stimulates and promotes the formation of liver glycogen via the PI3K/Akt/GSK3-glycogen synthase signaling pathway, which helps to maintain

glucose homeostasis in mice. Similar results demonstrated the prevention of glucosamine (GlcN) or palmitate-induced primary hepatocyte insulin resistance by irisin-activated phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/forkhead box protein O1 (FOXO1)-mediated PEPCK and G6Pase.[90]

Irisin may be crucial in several diseases, such as obesity, insulin sensitivity, and type 2 diabetes (T2DM).[91] In addition to insulin resistance, type 2 diabetes, cardiovascular disease, and cancer, obesity is a state of excessive fat storage [92]. In the serum of obese individuals, the irisin levels changed. Previous research found that obese people have lower levels of irisin, which may be related to poor PGC-1α expression in muscle.[82] Although other recent research reported the contrary, that irisin levels were higher in obese people,[93,94] this rise in irisin may be a compensatory answer to a decline in expenditure of energy. It is also conceivable that these individuals' increased adipose tissue might serve as an additional source of irisin.[95] It's possible that irisin resistance develops as obesity progresses, which might account for the participants' higher irisin levels.[93]

Additionally, irisin and adiposity indicators (BMI) have a favorable correlation.[96] After losing weight, significant improvements were observed in the lipid profile, fasting glucose, and body composition of those with initial irisin's high levels. These findings suggest that increased irisin regulates obesity, glucose control, and insulin resistance in a beneficial way.[97] In a different investigation, the circulating irisin and BMI had an antagonistic relationship.[82]

The process of obesity development may be associated with development of irisin resistance, which might explain the participants' increased irisin levels.[93] Irisin resistance is characterized by an elevated level of irisin in obese people to maintain the energy balance and preserve glucose homeostasis. To enhance anti-hyperglycemic and anti-obesity benefits of the irisin hormone, it is believed that hyperiricinemia, which is present in obese people, may be a mechanism.[98]

The amount of circulating irisin in a prior investigation on diabetes patients was shown to be considerably lower than that of the control group, and FNDC5/irisin treatment alleviated insulin resistance and glucose problems.[99] Additionally, it could signify a novel therapeutic strategy for the treatment of obesity because exercise and body weight loss affect the kinetics of irisin [97]. Glucose and lipid homeostasis are two of irisin's most significant and promising effects. The primary metabolic effects due to irisin are a decrease weight loss, hepatic insulin resistance, promotion of glycogenesis, decreased blood sugar levels, and suppression of gluconeogenesis.[31,100,101]

Irisin's function in the central nervous system

Researchers found that increased levels of ROS and malondialdehyde in peri-infarct brain tissues were reduced by irisin treatment in addition to improving the nerve function injury and cerebral infarction volume in the brain ischemia state, where irisin's level was negatively correlated with injury score and cerebral infarction volume.[102,103] In a cerebral ischemia of mouse model, irisin decreased oxidative stress-induced neuronal damage by reducing the release of proinflammatory cytokines such as IL-6 and tumor necrosis factor (TNF) through the Akt/ERK1/2 signaling pathway. [102]

Irisin is crucial to the brain and neurological system.[104] Irisin has been found in cerebrospinal fluid and hypothalamus, while FNDC5 is a protein that is known to be highly expressed in glia (such as astrocytes and microglia) and neurons in different parts of the brain [39]. Irisin is found in intercellular nerve terminals and cerebellar Purkinje cells [13,105]. It is now known that integrin V/b5 exists in the hippocampus and cortex[106], indicating that irisin collaborates with integrin αV/ b5 to protect the brain.[102]

Irisin plays both peripheral and central functions and is believed to act as a molecular bridge between the brain and muscles. Irisin is likely transported from the cerebellum to adipocytes through intermediary synapses in the medulla and spinal cord via a neurological pathway.[72] Irisin has beneficial effects on

nervous system by promoting the growth of hippocampal neurons [107] (high concentrations of irisin promote neuronal proliferation) [72], and the expression of brain-derived neurotrophic factor (BDNF), a factor that is also increased after exercise in neurodegenerative disorders [108,109]. It also plays a significant role in controlling feeding behavior.[14]

Irisin may support neuronal development by regulating CNS metabolic responses, according to one research [110]. Irisin improves brain function by modifying neurotransmitter release, according to recent research [111,112]. Exercises elevate mood, and more recently, it was thought that they may possibly have antidepressant properties due to changes in the prefrontal cortex's energy metabolism. [113] Irisin, a myokine with low levels linked to mood swings, may potentially play a role in this impact in addition to serotonin. The PGC-1α/BDNF pathway's activation is most likely what causes irisin to have this impact [114, 115].

Parkinson's disease (PD) is characterized by several pathological features, including abnormal α-synuclein intraneuronal aggregation, abnormal synaptic transmission, dysfunction of mitochondria and lysosomes, abnormal brain metabolism, and neuroinflammation. Additionally, the substantia nigra pars compacta loses its dopaminergic neurons. Exercise's positive effects on brain function may be mediated by irisin, as it has the ability to pass the blood-brain barrier. In preclinical mice, exogenous irisin treatment enhances motor results while reducing dopaminergic neuron degeneration and brain α-syn pathology.[116] Other biological effects of irisin, including neuronal differentiation, enhancements to cognition and memory, and preservation of synaptic plasticity have been demonstrated by further preclinical research.[61,117,118]

According to Kam et al., one explanation for the therapeutic advantages of exercise for those with Parkinson's disease [117]. This study was special because irisin was administered to PD model under test directly, as opposed to being produced by exercise.[119] The investigation gives mechanistic evidence indicating that irisin's ability to avert neuronal death and reduce α-syn diseases involves at least three pathways: a reduction in α-syn internalization by neurons, downregulation of ApoE4, and endolysosomal destruction of α-syn.[117] An earlier investigation using cellular pathway analysis on mice revealed that the effects of irisin injection on the brain proteome are comparable to those of exercise.[119] Since these diseases share similar underlying pathogenetic mechanisms with PD, such as protein misfolding and aggregation, neuroinflammation, metabolic abnormalities, vascular abnormalities, and neuronal loss, the encouraging results Kam et al. presented on irisin’s effects in PD may also be essential in context of other neurodegenerative disorders like Alzheimer's disease, multiple sclerosis (MS), and Huntington’s disease (HD).[120-122]

Alzheimer’s disease commonly referred to as AD, is characterized by formation of senile plaques as result of amyloid beta accumulation in the brain, oxidative stress, and progressive memory loss [39]. Clinical research has shown that obesity impairs cognitive performance, causes damages blood-brain barrier, white matter atrophy, and raises the risk of Alzheimer disease [123–125]. In Alzheimer disease animals, Lourenco et al. showed that FNDC5/irisin expression was downregulated in their hippocampi and CSF fluid. A unique medicinal agent that can enhance memory, learning, and cognitive function is FNDC5/irisin. [118]

The potential benefit of irisin as a treatment for AD. The first effect of irisin is to increase BDNF synthesis, which may then improve synaptic plasticity and memory in Alzheimer disease [38]. Second, irisin could promote neurogenesis and guard against neuronal deterioration in Alzheimer disease. Last but not least, irisin may control insulin resistance and glucose balance in AD.[39]

Increased inflammatory reactions in blood vessels cause synaptic plasticity to decline and hinder neurogenesis.[126] According to earlier research, irisin therapy may reduce the production of pro-inflammatory cytokines like TNF-alpha and IL-6 and cause macrophages to phenotypically flip from the pro-inflammatory M1 state to the anti-inflammatory M2 state.[127]

Role of irisin in osteoporosis

Irisin's primary target is thought to be bone tissue. Irisin has an impact on osteoclasts, osteoblasts, and osteocytes all in different ways. [128,129] Compared to adipose tissue, bone tissue responds to irisin's actions more responsive. [72]. The regulation of irisin on bone during exercise was mediated by irisin receptor integrin αV.[130] Irisin can prevent osteoclast development while increasing the proliferation of osteoclast precursor cells [131]. Based on direct action on osteoclast progenitors to enhance differentiation and stimulate bone resorption, irisin may be an important counter-regulatory hormone in addition to increasing bone remodeling, according to one study.[98]

Irisin has a beneficial impact on bones because it encourages bone generation, inhibits steroid-induced apoptosis, speeds up the healing of fractures, and promotes osteoblast differentiation.[19,132] The skeleton undergoes anabolic effects from irisin. Bone mineral density, also known as BMD, and bone strength have been shown to favorably correlate with irisin levels in athletes.[72] The association between plasma irisin and BMD suggests that bone and muscle have an innate connection.[80,134] In mice, FNDC5/irisin removal in the osteoblast lineage led to a decrease bone density and a delay in the formation and mineralization of new bones.[135]

To explain these results, different biological pathways may be suggested. Irisin first affects bone marrow stromal cells' ability to develop into mature osteoblasts..[81] Second, irisin may promote the maturation of bone marrow stem cells into osteoblasts, promoting the release of osteokines that stimulate the formation of new bone.[77] Additionally, irisin influences osteoblasts by promoting bone-forming cell development and activity by upregulating transcription factor 4 expression. The Wnt-b-catenin signaling pathway was activated by irisin to increase osteoblast development, whereas the RANK/RANKL pathway was suppressed to inhibit osteoclast differentiation.[136] In another investigation, it was demonstrated that irisin limited osteoclast differentiation by reducing the RANKL-Akt1/MITF/PU1-NFATc1 pathway while it also promoted osteoblast differentiation through the bone morphogenic protein (BMP) path.[137] Irisin increased p38 mitogen-activated protein kinase and extracellular signal-regulated kinase activity, which in turn increased osteoblast proliferation, alkaline phosphatase activity, differentiation, and mineralization in cultured osteoblasts.[138] This makes irisin a potential therapeutic target for bone disorders like osteoporosis and a modulator of the therapeutic benefits of exercise on the skeleton.[139,140]

Role of irisin in oxidative stress

Long-term hyperglycemia and insulin resistance may result in difficulties by harming organs including the kidneys, liver, eyes, nerves, and cardiovascular system through oxidative stress and an increase in the formation of reactive oxygen species (ROS) and free radicals. Where ROS and Malondialdehyde MDA (the biomarker of oxidative stress) enhance damage to lipids, cellular proteins, receptors, and DNA and may promote cell death by inducing lipid peroxidation.[141]

There is an unfavorable association between oxidative stress and irisin levels, according to recent studies.[142] Many chronic disorders, which are linked to chronic inflammation and persistent are at risk for development when there is a lack of physical exercise. Regular, moderate exercise has a good impact on immune system performance and decreases systemic inflammation [143]. Irisin controls the activation of immune-competent cells and lowers the formation of (ROS) without impacting cell survival, according to study on RAW 264.7 macrophages.[144] The enhanced production of important antioxidant enzymes, including as catalase 9, glutathione peroxidase, and superoxide dismutase, is the cause of irisin's antioxidative action.[145]

The amount of mitochondrial ROS and inflammatory substances significantly decreased after irisin therapy.[22] Irisin treatment enhanced PRAT UCP-1 and SIRT1, which suggests the browning of PRAT. This transdifferentiation encourages a number of factors that alter metabolism, including the antioxidant

protein HO-1, which guards against renal and cardiovascular disease due to its potent anti-oxidative and anti-inflammatory characteristics.[102] By reducing ROS generation and inflammation, this route is activated, which increases NO bioavailability by preventing peroxynitrite from being formed from NO.[146,147]

Conclusions

Irisin is a myokine, expressed mainly in skeletal muscles, and has significant biological effects in the inflammatory response, growth, and metabolic processes. Its main role is browning white adipose tissue by increasing the expression of UPC-1 pumps in mitochondria, which inhibits the formation of ATP and increases heat generation, thus increasing energy consumption in cells through β-oxidation and maintenance of body temperature.

The production of irisin is stimulated through exercise, cold, diet, and hormonal regulation. When the muscles contract during exercise, level of cytoplasmic Ca^{+2} is increased, thus AMPK phosphorylation increases, which increases the transcription cofactor PGC-1α in skeletal muscles and regulates the transcription of the FNDC5 protein. Irisin is the out-membrane of FNDC5 protein, where it is released to the bloodstream through proteolysis action by metalopiptidase after the enzyme-controlled glycosylation process, which aims to stabilize the protein and perform its biological function. Thus, molecular weight has increased from 12 to 15 kD. Hormone levels in the blood are affected by many disorders and diseases, such as cancer, type 2 diabetes, obesity, and Alzheimer.

No receptors have been discovered for irisin yet, but it does its function by attaching to integrin receptors, especially αV integrin.

Irisin reduces the generation and release of pro-inflammatory cytokines from adipose tissues and increases the release of anti-inflammatory cytokines like TNF and IL-6 [81, 73], resulting in reducing inflammation caused by obesity. It also inhibits gluconeogenesis by activating the AMPK-PEPCK-G-6-Pase pathway and stimulates the formation of glycogen in the liver to maintain glucose hemostasis. As for hormone levels in obese individuals, the results were unclear. Choi et al. indicated a lower serum level of hormone [82] due to lower expression of PGC-1α, but recent studies [93.94] indicated an increase in the level of hormone in the serum.

Additionally, irisin is present in the brain, where it can cross the brain-blood barrier and contribute to many processes such as food behavior, mood and memory improvement, learning, neurological differentiation, and rescue of synaptic plasticity. It also reduces oxidative stress, which causes neurological damage, by reducing pro-inflammatory cytokines.

Bones are a major target of irisin; it contributes to development and proliferation of osteoblast precursor cells, as well as accelerating the recovery from fractions and regulating the density of minerals in bones.

Conflicts of interest

There are no conflicts to declare.

References

1. NCBI. Fibronectin type III domain-containing protein 5 isoform 2 preproprotein [Homo sapiens]. NCBI; 2016.
2. Roca-Rivada A, et al. FNDC5/irisin is not only a myokine but also an adipokine. PLoS ONE. 2013; 8:e60563.

3. Schumacher MA, Chinnam N, Ohashi T, Shah RS, Erickson HP. The structure of irisin reveals a novel intersubunit β-sheet fibronectin type III (FNIII) dimer: implications for receptor activation. J Biol Chem. 2013; 288:33738–33744.
4. Johnson, R.W.; White, J.D.;Walker, E.C.; Martin, T.J.; Sims, N.A. Myokines (muscle-derived cytokines and chemokines) including ciliary neurotrophic factor (CNTF) inhibit osteoblast di_erentiation. Bone 2014, 64, 47–56.
5. Di Raimondo, D.; Miceli, G.; Musiari, G.; Tuttolomondo, A.; Pinto, A. New insights about the putative role of myokines in the context of cardiac rehabilitation and secondary cardiovascular prevention. Ann. Transl. Med. 2017, 5, 300.
6. Huh JY, et al. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism. 2012; 61:1725–1738.
7. Kurdiova T, et al. Effects of obesity, diabetes and exercise on Fndc5 gene expression and irisin release in human skeletal muscle and adipose tissue: in vivo and in vitro studies. J Physiol. 2014; 592:1091–1107.
8. Ferrer-Martínez A, Ruiz-Lozano P, Chien KR. Mouse PeP: a novel peroxisomal protein linked to myoblast differentiation and development. Dev Dynam 2002;224 (2):154–67.
9. Boström, Pontus, et al. "A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis." *Nature* 481.7382 (2012): 463-468.
10. Stratigou T, Dalamaga M, Antonakos G, Marinou I, Vogiatzakis E, Christodoulatos GS, Karampela I, Papavassiliou AG. Hyperirisinemia is independently associated with subclinical hypothyroidism: correlations with cardiometabolic biomarkers and risk factors. Endocrine 2018;61(1):83–93.
11. Pukajło, K.; Kolackov, K.; Łaczma´ nski, Ł.; Daroszewski, J. Irisin – a new mediator of energy homeostasis. Postepy Hig. Med. Dosw. 2015, 69, 233–242.
12. Norman D, Drott CJ, Carlsson PO, Espes D. Irisin-A Pancreatic Islet Hormone. Biomedicines. 2022 Jan 25;10(2):258. doi: 10.3390/biomedicines10020258.
13. Aydin, S.; Kuloglu, T.; Aydin, S.; Kalayci, M.; Yilmaz, M.; Cakmak, T.; Albayrak, S.; Gungor, S.; Colakoglu, N.;Ozercan, I.H. A comprehensive immunohistochemical examination of the distribution of the fat-burning protein irisin in biological tissues. Peptides 2014, 61, 130–136.
14. Leustean, L.; Preda, C.; Teodoriu, L.; Mihalache, L.; Arhire, L.; Ungureanu, M.-C. Role of Irisin in Endocrine and Metabolic Disorders—Possible New Therapeutic Agent? *Appl. Sci.* 2021, *11*, 5579.
15. Pedersen BK, Akerstrom TC, Nielsen AR, Fischer CP (2007) Role of myokines in exercise and metabolism. J Appl Physiol (1985) 103(3):1093–1098.
16. Ugur K, Aydin S (2019) What is the actual molecular weight of irisin hormone according to western blot analysis? Biochem Mod Appl 2:40–41
17. KÜÇÜKKARACA, Hazal, and Mehtap ÜNLÜ SÖĞÜT. "Investigation of the Effect of Exercise on Irisin Hormone in Experimentally Induced Diabetic Rats. " *International Journal of Health Services Research and Policy* 2.2 (2017): 51-57.
18. Fu, Jinjuan, et al. "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 (2016): e003433.

19. Korta, Paulina, Ewa Pocheć, and Agnieszka Mazur-Biały. "Irisin as a multifunctional protein: implications for health and certain diseases." *Medicina* 55.8 (2019): 485.

20. Provatopoulou, Xeni, et al. "Serum irisin levels are lower in patients with breast cancer: association with disease diagnosis and tumor characteristics." *BMC cancer* 15 (2015): 1-9.

21. Altay, D.U.; Keha, E.E.; Karagüzel, E.; Mente¸se, A.; Yaman, S.O.; Alver, A. The Diagnostic Value of FNDC5/Irisin in Renal Cell Cancer. Int. Braz. J. Urol. 2018, 44, 734–739.

22. Liu, Shiqiang, et al. "Role of irisin in physiology and pathology." *Frontiers in Endocrinology* 13 (2022): 962968.

23. Shao, Lei, et al. "Irisin suppresses the migration, proliferation, and invasion of lung cancer cells via inhibition of epithelial-to-mesenchymal transition." *Biochemical and biophysical research communications* 485.3 (2017): 598-605.

24. Zhu T, Zhang W, Zhang Y, Lu E, Liu H, Liu X, et al. Irisin/FNDC5 inhibits the epithelial-mesenchymal transition of epithelial ovarian cancer cells via the PI3K/Akt pathway. Arch Gynecol Obstet (2022) 306(3):841–850.

25. Liu, J.; Song, N.; Huang, Y.; Chen, Y. Irisin inhibits pancreatic cancer cell growth via the AMPK-mTOR pathway. Sci. Rep. 2018, 8, 15247.

26. Kong, Gang, et al. "Irisin reverses the IL-6 induced epithelial-mesenchymal transition in osteosarcoma cell migration and invasion through the STAT3/Snail signaling pathway." *Oncology reports* 38.5 (2017): 2647-2656.

27. Huang CW, Chang YH, Lee HH, Wu JY, Huang JX, Chung YH, et al. Irisin, an exercise myokine, potently suppresses tumor proliferation, invasion, and growth in glioma. FASEB J (2020) 34(7):9678–93.

28. Gannon, Nicholas P., et al. "Effects of the exercise-inducible myokine irisin on malignant and non-malignant breast epithelial cell behavior in vitro." *International journal of cancer* 136.4 (2015): E197-E202.

29. Park EJ, Myint PK, Ito A, Appiah MG, Darkwah S, Kawamoto E, et al. Integrin-ligand interactions in inflammation, cancer, and metabolic disease: Insights into the multifaceted roles of an emerging ligand irisin. Front Cell Dev Biol (2020) 8:588066.

30. Panati, K.; Narala,V.R.; Narasimha,V.R.; Derangula, M.; Arva Tatireddigari,V.R.R.; Yeguvapalli, S. Expression, purification and biological characterisation of recombinant human irisin (12.5 kDa). J. Genet. Eng. Biotechnol.2018, 16, 459–466.

31. Mahgoub, M.O.; D'Souza, C.; Al Darmaki, R.S.M.H.; Baniyas, M.M.Y.H.; Adeghate, E. An update on the role of irisin in the regulation of endocrine and metabolic functions. Peptides 2018, 104, 15–23.

32. Tsuchiya, Y.; Ando, D.; Goto, K.; Kiuchi, M.; Yamakita, M.; Koyama, K. High-intensity exercise causes greater irisin response compared with low-intensity exercise under similar energy consumption. Tohoku J. Exp. Med. 2014, 233, 135–140.

33. Tsuchiya, Y.; Ando, D.; Takamatsu, K.; Goto, K. Resistance exercise induces a greater irisin response than endurance exercise. Metabolism 2015, 64, 1042–1050.

34. Greulich, T.; Nell, C.; Koepke, J.; Fechtel, J.; Franke, M.; Schmeck, B.; Haid, D.; Apelt, S.; Filipovic, S.;Kenn, K.; et al. Benefits of whole body vibration training in patients hospitalised for COPD exacerbations—A randomized clinical trial. BMC Pulm. Med. 2014, 14, 60.

35. Varela-Rodríguez, B.M.; Pena-Bello, L.; Juiz-Valiña, P.; Vidal-Bretal, B.; Cordido, F.; Sangiao-Alvarellos, S. FNDC5expression and circulating irisin levels are modified by diet and hormonal conditions in hypothalamus, adipose tissue and muscle. Sci. Rep. 2016, 6, 29898.

36. 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.; et al. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. Cell Metab. 2014, 19, 302–309.

37. Moreno-Navarrete, J.M.; Ortega, F.; Serrano, M.; Guerra, E.; Pardo, G.; Tinahones, F.; Ricart, W.; Fernández-Real, J.M. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. J. Clin. Endocrinol. Metab. 2013, 98, E769–778.

38. Fukushima, Y., Kurose, S., Shinno, H., Cao Thi Thu, H., Tamanoi, A., Tsutsumi, H., et al, Relationships between serum irisin levels and metabolic parameters in Japanese patients with obesity, *Obes Sci Pract, 2* (2016), 2, pp. 203-209.

39. Kim, Oh Yoen, and Juhyun Song. "The role of irisin in Alzheimer's disease." *Journal of clinical medicine* 7.11 (2018): 407.

40. Yano, Naohiro, Yu Tina Zhao, and Ting C. Zhao. "The physiological role of irisin in the regulation of muscle glucose homeostasis." *Endocrines* 2.3 (2021): 266-283.

41. Berberoğlu, Hatice, and Aysun HACIŞEVKİ. "AN OVERVIEW OF THE EFFECTS OF IRISIN ON METABOLIC DISORDERS." *Gazi Sağlık Bilimleri Dergisi* 6.2 (2021): 33-41.

42. Aydin, S., Three new players in energy regulation: preptin, adropin and irisin, *Peptides*, *56* (2014), pp. 94-110.

43. Elbelt U, Hofmann T, Stengel A. Irisin: what promise does it hold? Curr Opin Clin Nutr Metab Care. 2013; 16:541–547.

44. Huh JY, Siopi A, Mougios V, Park KH, Mantzoros CS. Irisin in response to exercise in humans with and without metabolic syndrome. J Clin Endocrinol Metab. 2015; 100:E453–E457.

45. Handschin, C.; Spiegelman, B.M. Peroxisome proliferator-activated receptor gamma coactivator 1 coactivators, energy homeostasis, and metabolism. Endocr. Rev. 2006, 27, 728–735.

46. Jessen N, Goodyear LJ. Contraction signaling to glucose transport in skeletal muscle. J Appl Physiol (2005) 99(1):330–7. doi: 10.1152/japplphysiol.00175.2005

47. Shan T, Liang X, Bi P, Kuang S. Myostatin knockout drives browning of white adipose tissue through activating the AMPK-PGC1alpha-Fndc5 pathway in muscle. FASEB J (2013) 27(5):1981–9.

48. Ge X, Sathiakumar D, Lua BJ, Kukreti H, Lee M, McFarlane C. Myostatin signals through miR-34a to regulate Fndc5 expression and browning of white adipocytes. Int J Obes (Lond) (2017) 41(1):137–48.

49. Teufel, A.; Malik, N.; Mukhopadhyay, M.; Westphal, H. Frcp1 and Frcp2, two novel fibronectin type III repeat containing genes. Gene 2002, 297, 79–83. [

50. Korta, P.; Poche´c, E. Glycosylation of thyroid-stimulating hormone receptor. Endokrynol. Pol. 2019, 70, 86–100.

51. Nie, Y.; Liu, D. N-Glycosylation is required for FDNC5 stabilization and irisin secretion. Biochem. J. 2017, 474, 3167–3177.

52. Tan, N.Y.; Bailey, U.M.; Jamaluddin, M.F.; Mahmud, S.H.; Raman, S.C.; Schulz, B.L. Sequence-based protein stabilization in the absence of glycosylation. Nat. Commun. 2014, 5, 3099.

53. Zhang, Y.; Li, R.; Meng, Y.; Li, S.; Donelan, W.; Zhao, Y.; Qi, L.; Zhang, M.; Wang, X.; Cui, T.; et al. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes 2014, 63, 514–525.

54. Yu Q, Kou W, Xu X, Zhou S, Luan P, Xu X, et al. FNDC5/Irisin inhibits pathological cardiac hypertrophy. Clin Sci (Lond) (2019) 133(5):611–27.

55. 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. Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry.Cell Metab. 2015, 22, 734–740.

56. Askari, H.; Rajani, S.F.; Poorebrahim, M.; Haghi-Aminjan, H.; Raeis-Abdollahi, E.; Abdollahi, M. A glance at the therapeutic potential of irisin against diseases involving inflammation, oxidative stress, and apoptosis: An introductory review. Pharmacol. Res. 2018, 129, 44–55.

57. Waseem, R.; Shamsi, A.; Mohammad, T.; Hassan, M.I.; Kazim, S.N.; Chaudhary, A.A.; Rudayni, H.A.; Al-Zharani, M.; Ahmad, F.; Islam, A. FNDC5/Irisin: Physiology and Pathophysiology. *Molecules* 2022, *27*, 1118.

58. Kim, H.; Wrann, C.D.; Jedrychowski, M.; Vidoni, S.; Kitase, Y.; Nagano, K.; Zhou, C.; Chou, J.; Parkman, V.A.; Novick, S.J.; et al. Irisin Mediates E_ects on Bone and Fat via _V Integrin Receptors. Cell 2018, 175, 1756–1768.

59. Takada, Y.; Ye, X.; Simon, S. The integrins. Genome Biol. 2007, 8, 215.

60. Czy˙ z, M. Regulacja ekspresji integryn. Acta Haematol. Pol. 2000, 31, 17–23.

61. Rabiee, F.; Lachinani, L.; Ghaedi, S.; Nasr-Esfahani, M.H.; Megraw, T.L.; Ghaedi, K. New insights into the cellular activities of Fndc5/irisin and its signaling pathways. Cell Biosci. 2020, 10, 51.

62. Bulucu Altunkaynak, BZ., Özbek, E., Yağ Dokusu Endokrin Bir Organ mıdır, *Dicle Tıp Dergisi, 32* (2005), 4, pp.211-217.

63. Coelho, M., Oliveira, T., Fernandes, R., Biochemistry of adipose tissue: an endocrine organ, *Arch Med Sci, 9* (2013), 2, pp. 191-200.

64. Li H, Qin S, Liang Q, Xi Y, Bo W, Cai M, et al. Exercise training enhances myocardial mitophagy and improves cardiac function via Irisin/FNDC5-PINK1/Parkin pathway in MI mice. Biomedicines (2021) 9(6):701.

65. Fenzl, A.; Kiefer, F.W. Brown adipose tissue and thermogenesis. Horm. Mol. Biol. Clin. Investig. 2014, 19, 25–37.

66. Lee, Y.H.; Mottillo, E.P.; Granneman, J.G. Adipose tissue plasticity fromWAT to BAT and in between. Biochim. Biophys. Acta 2014, 1842, 358–369.

67. Moonen, M.P.B.; Nascimento, E.B.; Van Marken Lichtenbelt, W.D. Human brown adipose tissue:Underestimated target in metabolic disease? Biochim. Biophys. Acta Mol. Cell Biol. Lipids 2019, 1864, 104–112.

68. Schulz, T.J.; Tseng, Y.H. Brown adipose tissue: Development, metabolism and beyond. Biochem. J. 2013, 453,167–178

69. Lidell, M.E.; Betz, M.J.; Enerbäck, S. Brown adipose tissue and its therapeutic potential. J. Intern. Med. 2014,276, 364–377.

70. Oguri Y, Shinoda K, Kim H, Alba DL, Bolus WR, Wang Q, et al. CD81 controls beige fat progenitor cell growth and energy balance via FAK signaling. Cell (2020) 182(3):563–77 e20. doi: 10.1016/j.cell.2020.06.021

71. Gouveia, M.C.; Vella, J.P.; Cafeo, F.R. A_onso Fonseca, F.L.; Bacci, M.R. Association between irisin and major chronic diseases: A review. Eur. Rev. Med. Pharmacol. Sci. 2016, 20, 4072–4077.

72. Grygiel-Górniak, B.; Puszczewicz, M. A review on irisin, a new protagonist that mediates muscle-adipose-bone-neuron connectivity. Eur. Rev. Med. Pharmacol. Sci. 2017, 21, 4687–4693.

73. Arhire LI, Mihalache L, Covasa M. Irisin : A Hope in Understanding and Managing Obesity and Metabolic Syndrome. Front Endocrinol. 2019;10(524):1–12.

74. Gizaw M, Anandakumar P, Debela T. A review on the role of irisin in insulin resistance and type 2 diabetes mellitus. J. Pharmacopuncture. 2017;20(4):235–242.

75. Colaianni G, Mongelli T, Cuscito C, Pignataro P, Lippo L, Spiro G, et al.Irisin prevents and restores bone loss and muscle atrophy in hind-limb suspended mice. Sci Rep (2017) 7(1):2811.

76. Dokumacioglu E, Iskender H, Sahin A, Erturk EY, Kaynar O. Serum levels of nesfatin-1 and irisin in obese children. Eur Cytokine Netw (2020) 31(1):39–43.

77. Stengel A, Hofmann T, G-S M, E U, Kobelt P, Klapp B. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity–correlation with body mass index. Peptides (2013) 39:125–30.

78. Nastos C, Kalimeris K, Papoutsidakis N, Tasoulis MK, Lykoudis PM, Thedoraki K, et al. Global consequences of liver ischemia/reperfusion injury. Oxid Med Cell Longev (2014) 2014:906965.

79. Bozkuş Y, Mousa U, Kırnap N, İyidir ÖT, Ramazanova L, Nar A, ve ark. Kadınlarda metabolik sendromun alternatif prediktörleri. Pam Tıp Derg. 2020;13(2):341–349.

80. Tabak O, Simsek G, Erdenen F, Sozer V, Hasoglu T, Gelisgen R, ve ark. The relationship between circulating irisin, retinol binding protein-4, adiponectin and inflammatory mediators in patients with metabolic syndrome. Arch Endocrin Metab. 2017;61(6):515–523.

81. Mazur-Bialy, A.I.; Bilski, J.; Pochec, E.; Brzozowski, T. New insight into the direct anti-inflammatory activity of a myokine irisin against proinflammatory activation of adipocytes: Implication for exercise in obesity. J. Physiol. Pharmacol. 2017, 68, 243–251.

82. Choi Y, Kim M, Bae K, Seo H, Jeong J, Lee W, et al. Serum irisin levels in new-onset type 2 diabetes. Diabetes Res Clin Pract. 2013;100(1):96–101.

83. do Carmo Martins, M.; Faleiro, L.L.; Fonseca, A. Relationship between leptin and body mass and metabolic syndrome in an adult population. Rev. Port. Cardiol. 2012, 31, 711–719.

84. Gutierrez-Repiso, C.; Garcia-Serrano, S.; Rodriguez-Pacheco, F.; Garcia-Escobar, E.; Haro-Mora, J.J.; Garcia-Arnes, J.; Valdes, S.; Gonzalo, M.; Soriguer, F.; Moreno-Ruiz, F.J.; et al. FNDC5 could be regulated by leptin in adipose tissue. Eur. J. Clin. Investig. 2014, 44, 918–925.

85. Choi, C.H.J.; Cohen, P. Adipose crosstalk with other cell types in health and disease. Exp. Cell Res. 2017, 360,6–11.

86. Zhu W, Sahar NE, Javaid HMA, Pak ES, Liang G, Wang Y, et al. Exerciseinduced irisin decreases inflammation and improves NAFLD by competitive binding with MD2. Cells (2021) 10(12):3306.

87. Huh, J.Y.; Panagiotou, G.; Mougios, V.; Brinkoetter, M.; Vamvini, M.T.; Schneider, B.E.; Mantzoros, C.S. FNDC5 and irisin in humans: I. predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism 2012, 61, 1725–1738.

88. Dua, A.; Hennes, M.I.; Hoffmann, R.G.; Maas, D.L.; Krakower, G.R.; Sonnenberg, G.E.; Kissebah, A.H. Leptin: A significant indicator of total body fat but not of visceral fat and insulin insensitivity in African-American women. Diabetes 1996, 45, 1635–1637.

89. Xin C, Liu J, Zhang J, Zhu D, Wang H, Xiong L, et al. Irisin improves fatty acid oxidation and glucose utilization in type 2 diabetes by regulating the AMPK signaling pathway. Int J Obes (Lond) (2016) 40(3):443–51.

90. Liu TY, Shi CX, Gao R, Sun HJ, Xiong XQ, Ding L, et al. Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes. Clin Sci (Lond) (2015) 129 (10):839–50.

91. Al-Daghri, N.M.; Mohammed, A.K.; Al-Attas, O.S.; Amer, O.E.; Clerici, M.; Alenad, A.; Alokail, M.S. SNPs in FNDC5 (irisin) are associated with obesity and modulation of glucose and lipid metabolism in Saudi subjects. Lipids Health Dis. 2016, 15, 54.

92. Meilianna, A.; Dewi, N.M.; Wijaya, A. Adipose tissue, inflammation (Meta-inflammation) and Obesity management. Indones. Biomed. J. 2015, 7, 129–146.

93. Sahin-Efe, A.; Upadhyay, J.; Ko, B.J.; Dincer, F.; Park, K.H.; Migdal, A.; Vokonas, P.; Mantzoros, C. Irisin and leptin concentrations in relation to obesity, and developing type 2 diabetes: A cross sectional and a prospective case-control study nested in the Normative Aging Study. Metabolism 2018, 79, 24–32.

94. De Meneck, F.; de Souza, L.V.; Oliveira, V.; do Franco, M.C. High irisin levels in overweight/obese children and its positive correlation with metabolic profile, blood pressure, and endothelial progenitor cells. Nutr. Metab. Cardiovasc. Dis. 2018, 28, 756–764.

95. Rana, K.S.; Pararasa, C.; Afzal, I.; Nagel, D.A.; Hill, E.J.; Bailey, C.J.; Griffiths, H.R.; Kyrou, I.; Randeva, H.S.; Bellary, S.; et al. Plasma irisin is elevated in type 2 diabetes and is associated with increased E-selectin levels. Cardiovasc. Diabetol. 2017, 16, 147.

96. Elizondo-Montemayor, L.; Silva-Platas, C.; Torres-Quintanilla, A.; Rodríguez-López, C.; Ruiz-Esparza, G.U.; Reyes-Mendoza, E.; Garcia-Rivas, G. Association of irisin plasma levels with anthropometric parameters in children with underweight, normal weight, overweight, and obesity. Biomed. Res. Int. 2017, 2017, 2628968.

97. Fukushima, Y.; Kurose, S.; Shinno, H.; Thi Thu, H.C.; Takao, N.; Tsutsumi, H.; Hasegawa, T.; Nakajima, T.; Kimura, Y. Effects of body weight reduction on serum irisin and metabolic parameters in obese subjects. Diabetes Metab. J. 2016, 40, 386–395.

98. Perakakis N, Triantafyllou GA, Fernández-Real JM, Huh JY, Park KH, Seufert J, et al. Physiology and role of irisin in glucose homeostasis. Nat Rev Endocrinol. 2017 Jun;13(6):324-337.

99. Erdogan MA, Yalcin A. (2020) Protective effects of benfotiamine on irisin activity in methotrexateinduced liver injury in rats. Arch Med Sci 16(1):205-211.

100. Xiong, X.Q.; Chen, D.; Sun, H.J.; Ding, L.;Wang, J.J.; Chen, Q.; Li, Y.H.; Zhou, Y.B.; Han, Y.; Zhang, F.; et al. FNDC5 overexpression and irisin ameliorate glucose/lipid metabolic derangements and enhance lipolysis in obesity. Biochim. Biophys. Acta 2015, 1852, 1867–1875.

101. So, W.Y.; Leung, P.S. Irisin ameliorates hepatic glucose/lipid metabolism and enhances cell survival in insulin-resistant human HepG2 cells through adenosine monophosphate-activated protein kinase signaling. Int. J. Biochem. Cell. Biol. 2016, 78, 237–247.

102. Li DJ, Li YH, Yuan HB, Qu LF. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. Clin Exp (2017) 68:31–42. doi: 10.1016/j.metabol.2016.12.003

103. Gaggini, M.; Cabiati, M.; Del Turco, S.; Navarra, T.; De Simone, P.; Filipponi, F.; Del Ry, S.; Gastaldelli, A.; Basta, G. Increased FNDC5/Irisin expression in human hepatocellular carcinoma. Peptides 2017, 88, 62–66.

104. Dun, S.L.; Lyu, R.M.; Chen, Y.H.; Chang, J.K.; Luo, J.J.; Dun, N.J. Irisin-immunoreactivity in neural and non-neural cells of the rodent. Neuroscience 2013, 240, 155–162.

105. Piya, M.K.; Harte, A.L.; Sivakumar, K.; Tripathi, G.; Voyias, P.D.; James, S.; Sabico, S.; Al-Daghri, N.M.; Saravanan, P.; Barber, T.M.; et al. The identification of irisin in human cerebrospinal fluid: Influence of adiposity, metabolic markers, and gestational diabetes. Am. J. Physiol. Endocrinol. Metab. 2014, 306, E512–E518.

106. Jackson TC, Gorse K, Herrmann JR, Kochanek PM. Hippocampal and prefrontal cortical brain tissue levels of irisin and GDF15 receptor subunits in children. J Neurobiol (2021) 58(5):2145–57.

107. Moon, H.S.; Dincer, F.; Mantzoros, C.S. Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines. Metabolism 2013, 62, 1131–1136.

108. Huang H, Li W, Qin Z, Shen H, Li X, Wang W. Physical exercise increases peripheral brain-derived neurotrophic factors in patients with cognitive impairment: a meta-analysis. Restor Neurol Neurosci 2021;39(3):159–71.

109. Wrann CD. FNDC5/irisin - their role in the nervous system and as a mediator for beneficial effects of exercise on the brain. Brain Plast 2015;1(1):55–61.

110. Zhang,W.; Chang, L.; Zhang, C.; Zhang, R.; Li, Z.; Chai, B.; Li, J.; Chen, E.; Mulholland, M. Irisin: A myokine with locomotor activity. Neurosci. Lett. 2015, 595, 7–11.

111. Mattson, M.P. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Metab. 2012, 16, 706–722.

112. Erickson, K.I.; Weinstein, A.M.; Lopez, O.L. Physical activity, brain plasticity, and Alzheimer's disease. Arch.Med. Res. 2012, 43, 615–621.

113. Wang, S.; Pan, J. Irisin ameliorates depressive-like behaviors in rats by regulating energy metabolism. Biochem. Biophys. Res. Commun. 2016, 474, 22–28.

114. Wrann, C.D.; White, J.P.; Salogiannnis, J.; Laznik-Bogoslavski, D.;Wu, J.; Ma, D.; Lin, J.D.; Greenberg, M.E.; Spiegelman, B.M. Exercise induces hippocampal BDNF through a PGC-1_/FNDC5 pathway. Cell Metab.2013, 18, 649–659.

115. de Oliveira Bristot, V.J.; de Bem Alves, A.C.; Cardoso, L.R.; da Luz Sche_er, D.; Aguiar, A.S., Jr. The Role of PGC-1_/UCP2 Signaling in the Beneficial E_ects of Physical Exercise on the Brain. Front. Neurosci. 2019, 13,292.

116. Avgerinos, Konstantinos I., Junli Liu, and Maria Dalamaga. "Could exercise hormone irisin be a therapeutic agent against Parkinson's and other neurodegenerative diseases?." *Metabolism Open* (2023): 100233.

117. Kam TI, Park H, Chou SC, Van Vranken JG, Mittenbuhler MJ, Kim H, et al. Amelioration of pathologic alpha-synuclein-induced Parkinson's disease by irisin. Proc Natl Acad Sci U S A 2022;119(36):e2204835119.

118. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, et al. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med 2019;25(1):165–75.

119. Dehghan F, Zamani S, Barreiro C, Jami MS. Irisin injection mimics exercise effects on the brain proteome. Eur J Neurosci 2021;54(10):7422–41

120. Wareham LK, Liddelow SA, Temple S, Benowitz LI, di Polo A, Wellington C, Goldberg JL, He Z, et al. Solving neurodegeneration: common mechanisms and strategies for new treatments. Mol Neurodegener 2022;17(1):23.

121. Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. Nat Neurosci 2018;21(10):1332–40.

122. Kapogiannis D, Avgerinos KI. Brain glucose and ketone utilization in brain aging and neurodegenerative diseases. Int Rev Neurobiol 2020;154:79–110.

123. Droogsma, E.; van Asselt, D.; Bieze, H.; Veeger, N.; De Deyn, P.P. The relationship of weight change trajectory with medial temporal lobe atrophy in patients with mild Alzheimer's disease: Results from a cohort study. Alzheimer's Res. Ther. 2015, 7, 18.

124. Gustafson, D.R.; Luchsinger, J.A. High adiposity: Risk factor for dementia and Alzheimer's disease? Alzheimer's Res. Ther. 2013, 5, 57.

125. Sanz, C.M.; Ruidavets, J.B.; Bongard, V.; Marquie, J.C.; Hanaire, H.; Ferrieres, J.; Andrieu, S. Relationship between markers of insulin resistance, markers of adiposity, HbA1c, and cognitive functions in a middle-aged population-based sample: The MONA LISA study. Diabetes Care 2013, 36, 1512–1521.

126. Kiliaan, A.J.; Arnoldussen, I.A.; Gustafson, D.R. Adipokines: A link between obesity and dementia? Lancet Neurol. 2014, 13, 913–923.

127. Park, S.Y.; Kim, H.J.;Wang, S.; Higashimori, T.; Dong, J.; Kim, Y.J.; Cline, G.; Li, H.; Prentki, M.; Shulman, G.I.et al. Hormone-sensitive lipase knockout mice have increased hepatic insulin sensitivity and are protected from short-term diet-induced insulin resistance in skeletal muscle and heart. Am. J. Physiol. Endocrinol. Metab. 2005, 289, E30–E39.

128. Shoukry, A.; Shalaby, S.M.; El-ArabiBdeer, S.; Mahmoud, A.A.; Mousa, M.M.; Khalifa, A. Circulating serum irisin levels in obesity and type 2 diabetes mellitus. IUBMB Life 2016, 68, 544–556.

129. Al-Daghri, N.M.; Mohammed, A.K.; Al-Attas, O.S.; Amer, O.E.; Clerici, M.; Alenad, A.; Alokail, M.S. SNPs in FNDC5 (irisin) are associated with obesity and modulation of glucose and lipid metabolism in Saudi subjects. Lipids Health Dis. 2016, 15, 54.

130. Kawao N, Iemura S, Kawaguchi M, Mizukami Y, Takafuji Y, Kaji H, et al. Role of irisin in effects of chronic exercise on muscle and bone in ovariectomized mice. Jo Bone (2021) 39(4):547–57.

131. Pardo M, Crujeiras AB, Amil M, Aguera Z, Jiménez-Murcia S, Baños R, et al. Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. Int J Endocrinol. 2014;2014:857270.

132. Raschke, S.; Elsen, M.; Gassenhuber, H.; Sommerfeld, M.; Schwahn, U.; Brockmann, B. Evidence against a beneficial effect of irisin in humans. PLoS ONE 2013, 8, e73680.

133. Korta P, Pocheć E, Mazur-Biały A. Irisin as a multifunctional protein: Implications for health and certain diseases. Medicina (Lithuania). 2019;55(8):1–14.

134. Tang L, Tong Y, Zhang F, Chen G, Zhang YC, Jobin J, et al. The association of circulating irisin with metabolic risk factors in Chinese adults: A cross-sectional community-based study. BMC Endocr. Disord. 2019;19(1):1–6.

135. Zhu X, Li X, Wang X, Chen T, Tao F, Liu C, et al. Irisin deficiency disturbs bone metabolism. J Cell Physiol (2021) 236(1):664–76.

136. Colaianni, G.; Cuscito, C.; Mongelli, T.; Oranger, A.; Mori, G.; Brunetti, G.; Colucci, S.; Cinti, S.; Grano, M. Irisin enhances osteoblast differentiation in vitro. Int. J. Endocrinol. 2014, 2014, 902186.

137. Zhang J, Wu Y, Yu L et al: Exercise strengthens bone through myokine irisin. J Bone Miner Res, 2012; 27 (Suppl. 1): 1222

138. Chen, Zhihao, et al. "Recombinant irisin prevents the reduction of osteoblast differentiation induced by stimulated microgravity through increasing β-catenin expression." *International journal of molecular sciences* 21.4 (2020): 1259.

139. DiVasta, Amy D., and Catherine M. Gordon. "Exercise and bone: where do we stand?." *Metabolism-Clinical and Experimental* 62.12 (2013): 1714-1717.

140. Qiao YQ, Nie Y, Ma YX et al: Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways. Sci Rep, 2016; 6: 18732.

141. Erdogan, Mehmet Mustafa, et al. "Hepatoprotective effects of N-acetylcysteine on liver injury by irisin upregulation and oxidative stress reduction in diabetic rats." *Egyptian Liver Journal* 13.1 (2023): 1-9.

142. Zhu D, Wang H, Zhang J et al (2015) Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses. J Mol Cell Cardiol 87:138–147.

143. Handschin, C.; Spiegelman, B.M. The role of exercise and PGC1alpha in inflammation and chronic disease.Nature 2008, 454, 463–469.

144. Mazur-Bialy, A.I. Irisin acts as a regulator of macrophages host defense. Life Sci. 2017, 176, 21–25.

145. Mazur-Bialy, A.I.; Kozlowska, K.; Pochec, E.; Bilski, J.; Brzozowski, T. Myokine irisin-induced protection against oxidative stress in vitro. Involvement of heme oxygenase-1 and antioxidazing enzymes superoxide dismutase-2 and glutathione peroxidase. J. Physiol. Pharmacol. 2018, 69, 117–125.

146. Liu Y, Zhu C, Guo J, Chen Y, Meng C. The neuroprotective effect of irisin in ischemic stroke. Front Aging Neurosci (2020) 12:588958.

147. Uysal N, Yuksel O, Kizildag S, Yuce Z, Gumus H, Karakilic A, et al. Regular aerobic exercise correlates with reduced anxiety and incresed levels of irisin in brain and white adipose tissue. Front Aging Neurosci (2018) 676:92–7.