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Review Article

Irisin and its Effects on the Metabolic Diseases

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ABSTRACT

Irisin, also known as Fibronectin type III, is a hormone that is secreted by muscle cells and was first discovered in the muscles of a mouse in 2012. Irisin has a molecular weight of 23,231 KDa and belongs to the domain containing 5 (FNDC5) family. It has been shown to have some very beneficial effects in humans, such as thermoregulation and weight loss, and it is also secreted by the muscles of humans when they exercise or work out. The gene symbol for irisin is FNDC5, which represents the precursor of irisin. At the protein level, both FNDC5 and irisin have characteristics that are similar, but FNDC5 is not appropriate in some situations. It is released during physical activity and is linked to a variety of metabolic diseases such as obesity, type 2 diabetes, lipid metabolism, heart disease, NAFLD, PCOS, and metabolic diseases of the bones. Irisin is not only responsible for the disorders, but it also has the potential to be used as a biomarker for specific diseases. Humans and mice have both shown that myokine irisin promotes the browning of white adipose tissues while simultaneously increasing thermogenesis and energy expenditures. Irisin therapy reduces body weight while also increasing brown fat-specific gene expression in the patient. Irisin increases the risk of type 2 diabetes and cancer. Irisin levels were found to be lower in obese people who had NAFLD.

INTRODUCTION

Irisin is also given an additional name as Fibronectin type – III domain containing 5 (FNDC5). It was discovered a few years ago in 2012 in the muscles of mouse. Some very beneficial effects have been reported in the humans like thermoregulation and weight loss and is also secreted in the muscles of humans during exercise. Irisin is yield on cleavage of its originator Fibronectin type III domain containing 5 (FNDC5). The precursor FNDC5 weights about 23, 231 KDa. There is a difference in the KDa of transmembrane and cellular FNDC5, the cellule FNDC5 have molecular weight of 23KDa that is smaller than transmembrane having Molecular weight of 32 KDa. It has been well conserved through evolutionary process in the animals. Most of information about irisin has also been seen as similar in FNDC5 like gene and homology etc. [1]. It was reported that there is a protein that is formed by the cleavage of FNDC5 that is found in the cells of skeletal muscles. Browning of white fat is affected at a huge extent by this protein. After some days of continuous exercise, a huge increase in the volume of circulating irisin was also observed in both mice and humans [2]. The mineral density of bones is related to serum concentrations of irisin [3]. Some pathological conditions like osteoarthritis is also related to the lower serum concentrations of irisin [4]. Osteogenesis can also be induced by irisin; bone loss that is caused by the estrogen deficiency can be resisted by the deletion of FNDC gene.

Structure

Irisin mainly has three parts i.e., 29- amino acid signal peptide, 94- amino acid single FN III Fibronectin domain

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and C- terminal The insertion of irisin in human beings has been reported as 50- amino acid N-terminal [5]. Basic structure and activity of irisin is shown in Figure 1.

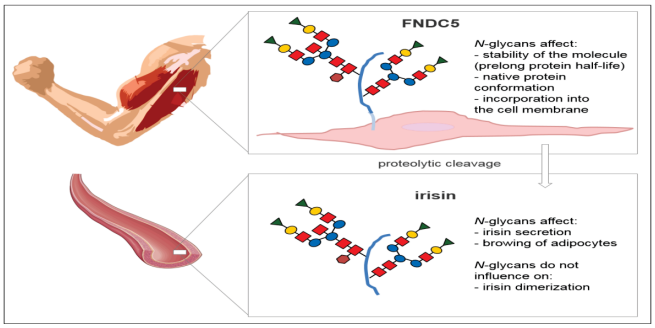

Figure 1: Showing the activity and the basic structure of irisin [6]

Origin of Irisin in the Human Body

The human FNDC5 gene's start codon was altered, and cells transfected with the mutant version of the gene translated only 1 % of the full-length protein [7]. Many scientists stated that translation of irisin is not started by a normal start codon (AUG) rather it is started by a manipulated start codon (non-canonical start codon). Animals having dense genetic arrangements like bacteria, fungi and mammalian cells that are affected by the viruses have the non-canonical start codons [8]. Non-canonical start codons have a much lower translational rate than the AUG start codon. The expression of proteins can be initiated by any of six non-canonical start codons [9]. Kim discovered three distinct FNDC5 transcripts with varying degrees of expression in various human tissues [10]. This is the first research to find irisin transcripts, and it will be the only one for the foreseeable future. Recent research, however, found that when employing all of the exons in these three transcripts, the annotated transcripts were not amplified [11]. Women suffering from osteoporosis have low serum irisin level [12]. Older women with minimal trauma hip fracture show lower serum irisin level and vice versa. For normal bone functioning irisin level is important and those having high hip density show high level of irisin [13]. In mice, bone formation rate is increased using recombinant irisin and it also alleviates the bone loss caused by ovariectomy and inflammatory disease in gastrointestinal tract. Irisin is sensitive to bone cells i.e. if a lower amount of irisin is introduced then it only effects the bone cells without browning of WAT [14]. Damage caused to bones because of disuse can also be restored with irisin [15]. Colaianni observed that differentiation of osteoblast promoted through irisin by MAPK and WNT pathways. Recombinant irisin act on osteoblast and activates 2 pathways i.e., P38 and ERK, the expression of ATF-4 increases and RUNX2 pathways activated [16]. The Wnt target genes activated when β-catenine moves in nucleus from cytoplasm [17].

Synthesis, Release and Regulation of Irisin

The precursor FNDC5 of irisin is the gene symbol for irisin. At protein level both FNDC5 and irisin show similarity in their characteristics but in some cases is not suitable. The gene responsible for the production of FNDC5 is located on the chromosome 1 in humans. The mRNA of FNDC5 in humans has 2099bp. The FNDC5 found in humans have 6 exons and 5 introns [18]. The transcriptional co-activator peroxisome proliferator-activated receptor-γ (PPAR γ) and the coactivator-1α (PGC1α), activate the gene expression of FNDC5. The cleavage and release of irisin is similar to the cleavage and release of transmembrane polypeptides in epidermal growth factor (EGF) and transforming growth factor-α (TGF- α). The C-terminal moiety is glycosylated and proteolytically cleaved to liberate the 112-aa hormone that contains most of the FNIII repeat region and release the hormone (Figure 2) [19].

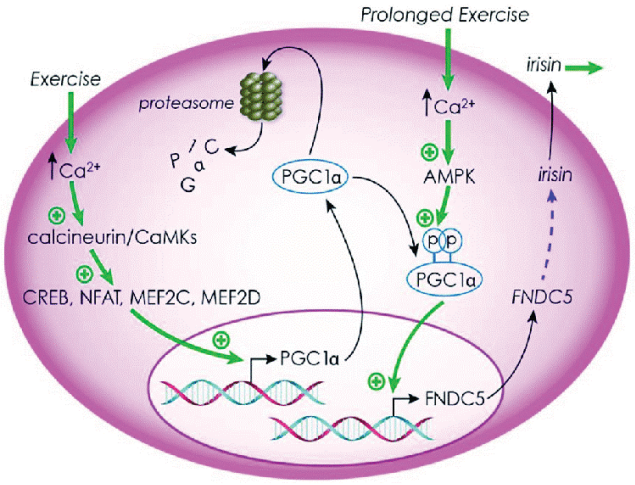

Figure 2: Showing the synthesis and release of irisin from muscle [20]

Irisin Detection Methods

Irisin is not only causing the disorders but can also be used as a biomarker for definite diseases [21]. ELISA is an antibody-antigen based detection method in human research, it is frequently utilized because of its quick detection speed, simple installation, and capacity to examine a large number of samples [22]. The irisin level in young athletes is tested higher than other individuals [23]. Ruan *et al.*, 2019 used both mass spectrometry and ELISA kits to examine the irisin level in cerebrospinal fluid but these kits failed to measure the irisin level in about 1/3rd of the sample while spectrometry measured it quantitatively [24]. The molecular weight of irisin was first calculated as 22kDa. The weight of irisin has ranged from 22 to 34 kDa, whereas the molecular weight was expected to be 12 kDa, Schumacher reported that irisin act like a dimer and its molecular weight by 24 kDa, which is not affected by glycosylation [25].

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Irisin in Metabolic Diseases

In both humans and mice, the myokine irisin promotes browning of white adipose tissues while also increasing thermogenesis and energy expenses. Irisin causes many metabolic diseases like obesity, T2DM, lipid metabolism, diseases related to heart, NAFLD, PCOS and metabolic diseases of bone [26]. Irisin is the new health promoting hormone because in human muscles, FNDC5 gene is expressed during exercise and produces irisin. Irisin causes browning of white fat that enhances the metabolic uncoupling and increases the energy expenses. Two pathways i.e. p38 mitogen-activated protein kinase (MPAK) and extra cellular-signal regulated kinas (ERK) enhance this metabolic uncoupling. The maturation of preadipocytes into mature adipocytes decreases after the treatment of irisin and the gene expression remain unaffected. The MPAK and ERK-p38 pathways are triggered due to the increase expression of UCP1 protein. Agetr cold exposure the insulin-mediated glucose uptake of BAT rises ten times more than WAT [23]. The earlier studies show that expression and activity of PGC-1α and irisin level is lower in patients having T2DM. It was concluded that patients suffering from T2DM have lower level of circulating irisin than the normal persons [27].

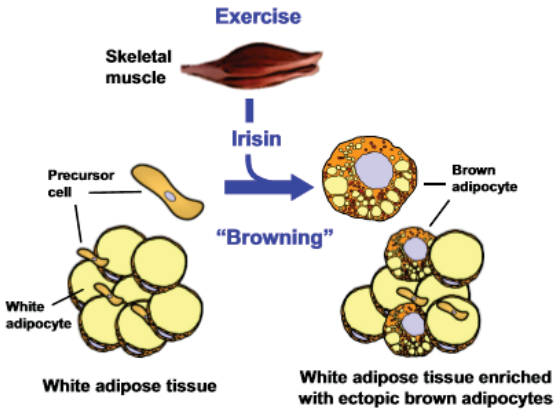

Figure 3: Showing the effect of irisin on adipose tissue [28]

Association between Serum Irisin Level and Exercise

Boström and colleagues reported that after exercise of about 10 weeks, the irisin level increases by 2 folds [29]. If the mouse runs downhill the level of irisin was reported to increases significantly but no change in the level of irisin was reported in uphill running after exercise of two weeks [30]. Changes that are induced by exercise are more complicated in patients suffering from metabolic disorders. In mice suffering from hyperthyroidism or hypothyroidism serum irisin level can be increased even after an acute exercise [31]. Huh reported that after 8 weeks of running there was no change in the serum irisin level in humans [5]. In later studies, it was observed that there is decrease in the level of serum irisin after a few weeks of exercise [32].

Stimulation of Browning of White Adipocytes

Ability of animals to resist body fat gain is connected to the quantity and activity of brown adipocytes. Some white adipose tissue (WAT) depots are easily converted into a "brown-like" state in particular circumstances, that is linked to mass decrease [33]. Irisin stimulates browning of WAT through unidentified mechanism. In mice, Recombinant irisin reduced body mass and improved glucose homeostasis [34]. Irisin increased the expression of uncoupling protein-1. Irisin-induced activation of the p38 MAPK and ERK signaling pathways may be responsible for this impact [35]. SB203580 and U0126 inhibition of the p38 MAPK and ERK inhibited upregulation of UCP-1 by irisin. Irisin also increased the expression of betatrophin, a recently discovered hormone that increases pancreatic β-cell proliferation and improves glucose tolerance [35]. Finally, our results show that irisin may help to reduce obesity and type 2 diabetes by increased expression of WAT browning-specific genes through the p38 MAPK and ERK pathways [36]. Obesity is by far the most common metabolic disorder that occurs in the world [37]. Obesity arises when a patient's calorie intake beyond their calorie expenditure, and it is defined by a rise in fatty tissue [38]. Overweight persons are more likely to get type 2 diabetes (T2DM) [39]. In terms of avoiding overweight, greater energy consumption has appeared as a possible and acceptable alternative [40]. While the exact mechanisms that control calorie expenditure are unknown, adipocytes play a very important role in mammalian energy balance and nutrient fluxes. White fat tissue and brown fat tissue are two kinds of adipose tissue that have received a lot of attention [41]. Brown adipocytes burn energy, whilst white adipocytes store it. Changes in BAT activity have been shown in numerous studies to have a significant impact on adaptive thermogenesis and glucose homeostasis [42]. Brown fat's thermogenic activity is primarily enabled by the presence of UCP-1, a mitochondrion uncoupling protein that decouples the electron transport chain from energy production, allowing potential energy received from food to be released as heat [43]. The transcriptional factor PPAR coactivator-1 (PGC-1), that can be stimulated by cold contact and/or -adrenergic signaling, regulates the expression of UCP-1 [44]. In various lab animals, browning of WAT compartments plays a protective role versus nutrition metabolic diseases like as obesity and diabetes [45]. It has 111 amino acids and a molecular weight of 22 kDa. PGC-1α and exercise have been shown to increase the expression of FNDC5, a type I transmembrane protein found in skeletal muscle. Irisin that is produced after Fndc5 is proteolyzed at amino acid positions 30 and 140. An increased level of irisin by an adenoviral vector enhances

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complete body energy expenditure, causes minor weight loss, and improves glucose intolerance in high fat–fed mice [2]. The circulating level is mostly determined by age and skeletal muscle mass, with irisin levels in young male athletes are many times higher than in middle-aged obese women [5]. When compared to non-diabetic control participants, circulating irisin is noticeably lower in people with T2DM [27]. Furthermore, in chronic renal disease patients [46], plasma irisin levels are inversely connected with blood urea nitrogen levels and favorably connected with aerobic act in heart failure patients. Irisin, like hepatic fibroblast growth factor 21 [47] and cardiac natriuretic peptides, can now be considered a secreted protein that stimulates brown adipocyte thermogenesis [48]. However, very little known about the molecular processes and signaling pathways that irisin employs to produce the active brown-like adipocyte phenotype. Li *et al.*, in their study, developed a productive technique for the synthesis and purification of human recombinant irisin (r-irisin), and administered the r-irisin to mice through intraperitoneal injection. To better comprehend the fundamental "browning" mechanisms, they used r-irisin to treat primary adipocytes and 3T3-L1-derived adipocytes and looked at how it impacted the browning of fat cells [49]. In line with earlier research [50], their results showed that r-irisin treatment reduces body mass, elevates brown fat-specific gene expression in subcutaneous white adipose tissue, and enhances glucose tolerance in vivo. In cell culture assays, irisin increased the expression of genes related to brown fat by activating the p38 MAPK and ERK pathways [51].

T2DM

Adipocyte browning has been shown to be controlled by irisin, although its effects on lipid and glucose metabolism in T2DM remain mainly unclear. In diabetic mice Irisin's involvement in glucose consumption and lipid metabolism was examined. There was an increase in 18F-FDG accumulation and GLUT4 translocation in diabetic skeletal muscle when irisin was improved. Similarly, in myocytes, irisin enhanced glucose absorption grown in a high glucose medium. PEPCK and G6Pase inhibited by insulin in diabetic liver [52]. Diabetes mice treated with irisin showed a reduction in fat mass, total cholesterol serum, and triglyceride levels, but a rise in acetyl coenzyme fat tissue UCP1 expression and a carboxylase β-phosphorylation. Myocytes' lipid acid oxidation was also enhanced by Irisin. Irisin's effects on consumption of glucose and fatty acid β-oxidation in myocytes were reduced when AMPK was repressed. In hepatocytes irisin effect reduced on PEPCK and G6Pase by the inhibition of AMPK by a specific inhibitor [53]. By managing endoplasmic reticulum (ER) strain, irisin can enhance hepatic glucose and lipid regulation. It also boosts islet-cell activity and survival, therefore alleviating hyperglycemia, hyperlipidemia, and insulin resistance. If verified, irisin may decrease these defects in hepatic and islet functioning, which efficiently reduce T2DM risk [54]. In hepatocytes, irisin inhibits lipogenesis induced by palmitic acid and gluconeogenesis induced by glucosamine, through the PRMT3 and PI3K/Akt pathways, respectively [55]. In obese people with NAFLD, blood irisin levels were lower, which was connected to content of hepatic triglyceride. The islets of liver and the pancreas play important roles in T2DM pathogenesis, and are vulnerable to glucoli-potoxicity. The exact mechanism from which irisin controls hepatic glucose and lipid homeostasis as well as protects beside islet malfunction and death is remain unknown [56].

Irisin and Cancer

Exercise has been shown to lower the risk of many forms of cancer, prevent cancer progression, and have beneficial and healing effects on cancer. Changes in physical composition, hormone secretion, severe inflammatory state, and the immunity have all been postulated as potential moderators of exercise's anti-cancer benefits [57]. Obesity enhances inflammatory markers (IL-6 and TNF-), glucose intolerance, and adipokine productions, which together favor cancer cell proliferation and survival, whereas exercise has shown that anti-inflammatory benefits by decreasing TNF- expression. Considering that irisin has been linked to obesity, it makes sense that it could also be linked to cancer [58]. Increased irisin levels reduced lung cancer cell production, capability, and invasiveness via influencing the EMT, dramatically lowering the EMT markers (N-cadherin and vimentin) while raising E-cadherin expression. The Snail pathway, which is mediated by the PI3K/Akt pathway, was associated to this reduction in EMT. Irisin's effect on the PI3K pathway may also imply an inhibiting effect, which may also explain why cancer cell growth has reduced [59]. Irisin could be a new biomarker for breast cancer detection. 90% risk of breast cancer is reduced by increasing blood irisin level; whereas breast cancer patient had much lower irisin serum levels than healthy individuals. When the breast tumor cells are exposed to irisin, the caspase-3/7 increases and NF-κB movement suppressed thus cause the decrease in number of tumor cells [60]. The impact of irisin was studied using three different types of cells: non-malignant breast epithelial cells, malignant breast epithelial cells, and malignant aggressive breast epithelial cells. When aggressive breast tumour cells were exposed to irisin, there was an increase in caspase 3/7 and a reduction of NF-kB. Irisin increases caspase 3 activation and apoptosis, as well as the ability to fight cell death [61]. When the cells were exposed to irisin, there was an increase in doxorubicin

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(a chemical reagent that is highly effective in cancer therapy) [62]. Irisin performs a protective role on bone against the breast cancer. It protects from the metastasis of breast cancer. Irisin and spinal irisin levels are inversely linked, indicating [60]. In osteocarcinoma cells irisin was able to inhibit the STAT3 pathway by reversing the IL-6-induced by [63]. Irisin's capacity to suppress EMT, capability, and growth of pancreatic cancer cell lines was further demonstrated when AMPK pathway is activated. Irisin suppresses the development of pancreatic cancer cells via the AMPK-mTOR pathway. Irisin's capacity to aim the AMPK pathway suggests that it may play a task in decreasing growth and modifying cancer metabolism [64]. Furthermore, irisin can be employed to detect for renal diagnosis of renal cancer, as irisin levels were significantly greater in individuals having kidney tumors; irisin also showed elevated particularly and sensitivity than other studied biomarkers [45]. The vitality of prostate cancer cells was lowered when different doses of irisin were applied to them [65]. In glioblastoma cells, irisin triggered G2/M cell cycle arrest and elevated p21 levels, inhibiting cell proliferation. Furthermore, through upregulating TFPI-2, irisin prevented glioblastoma cell invasion. Furthermore, irisin inhibited cancer in xenograft glioblastoma cells, and radiolabeled irisin revealed precise cancer cells-targeting capabilities in vivo.

CONCLUSIONS

As a result, our study identified irisin as a potential biochemical mechanism by which exercise reduces cancer progression. Irisin has the chance of growing as a molecular scanning and anticancer treatment drug.

Authors Contribution

Conceptualization: MFB, MKAK
Writing-review and editing: MFB, MKAK, M, MP, MA, UY, SS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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REFERENCES

[1] Aydin S. Three new players in energy regulation: preptin, adropin and irisin. Peptides. 2014 Jun; 56: 94-110. doi: 10.1016/j.peptides.2014.03.021.

[2] Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, *et al.* A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012 Jan; 481(7382): 463-8. doi: 10.1038/nature10777.

[3] Soininen S, Sidoroff V, Lindi V, Mahonen A, Kröger L, Kröger H, *et al.* Body fat mass, lean body mass and associated biomarkers as determinants of bone mineral density in children 6–8 years of age–The Physical Activity and Nutrition in Children (PANIC) study. Bone. 2018 Mar; 108: 106-14. doi: 10.1016/j.bone.2018.01.003.

[4] Yan J, Liu HJ, Guo WC, Yang J. Low serum concentrations of Irisin are associated with increased risk of hip fracture in Chinese older women. Joint Bone Spine. 2018 May; 85(3): 353-8. doi: 10.1016/j.jbspin.2017.03.011.

[5] Huh JY, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, Schneider BE, *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 Dec; 61(12): 1725-38. doi: 10.1016/j.metabol.2012.09.002.

[6] Korta P, Pocheć E, Mazur-Biały A. Irisin as a multifunctional protein: implications for health and certain diseases. Medicina. 2019 Aug; 55(8): 485. doi: 10.3390/medicina55080485.

[7] Peng H, Wang Q, Lou T, Qin J, Jung S, Shetty V, *et al.* Myokine mediated muscle-kidney crosstalk suppresses metabolic reprogramming and fibrosis in damaged kidneys. Nature Communications. 2017 Nov; 8(1): 1493. doi: 10.1038/s41467-017-01646-6.

[8] Eisenberg AR, Higdon AL, Hollerer I, Fields AP, Jungreis I, Diamond PD, *et al.* Translation initiation site profiling reveals widespread synthesis of non-AUG-initiated protein isoforms in yeast. Cell Systems. 2020 Aug; 11(2): 145-60. doi: 10.1016/j.cels.2020.06.011.

[9] Hecht A, Glasgow J, Jaschke PR, Bawazer LA, Munson MS, Cochran JR, *et al.* Measurements of translation initiation from all 64 codons in E. coli. Nucleic Acids Research. 2017 Apr; 45(7): 3615-26. doi: 10.1093/nar/gkx070.

[10] Kim HK, Jeong YJ, Song IS, Noh YH, Seo KW, Kim M, *et al.* Glucocorticoid receptor positively regulates transcription of FNDC5 in the liver. Scientific Reports. 2017 Feb; 7(1): 43296. doi: 10.1038/srep43296.

[11] Albrecht E, Schering L, Buck F, Vlach K, Schober HC, Drevon CA, *et al.* Irisin: Still chasing shadows. Molecular Metabolism. 2020 Apr; 34: 124-35. doi: 10.1016/j.molmet.2020.01.016.

[12] Anastasilakis AD, Polyzos SA, Makras P, Gkiomisi A, Bisbinas I, Katsarou A, *et al.* Circulating irisin is associated with osteoporotic fractures in postmeno-

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DOI: https://doi.org/10.54393/pbmj.v6i07.905

pausal women with low bone mass but is not affected by either teriparatide or denosumab treatment for 3 months. Osteoporosis International. 2014 May; 25: 1633-42. doi: 10.1007/s00198-014-2673-x.

[13] 13.Wu LF, Zhu DC, Tang CH, Ge B, Shi J, Wang BH, *et al.* Association of plasma irisin with bone mineral density in a large Chinese population using an extreme sampling design. Calcified Tissue International. 2018 Sep; 103: 246-51. doi: 10.1007/s00223-018-0415-3.

[14] Colaianni G, Cuscito C, Mongelli T, Pignataro P, Buccoliero C, Liu P, *et al.* The myokine irisin increases cortical bone mass. Proceedings of the National Academy of Sciences. 2015 Sep; 112(39): 12157-62. doi: 10.1073/pnas.1516622112.

[15] Tucci M, Stucci S, Felici C, Cafforio P, Resta L, Rossi R, *et al.* Cilengitide restrains the osteoclast-like bone resorbing activity of myeloma plasma cells. British Journal of Haematology. 2016 Apr; 173(1): 59-69. doi: 10.1111/bjh.13922.

[16] Qiao X, Nie Y, Ma Y, Chen Y, Cheng R, Yin W, *et al.* Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways. Scientific Reports. 2016 Jan; 6(1): 18732. doi: 10.1038/srep18732.

[17] Zhang J, Valverde P, Zhu X, Murray D, Wu Y, Yu L, *et al.* Exercise-induced irisin in bone and systemic irisin administration reveal new regulatory mechanisms of bone metabolism. Bone Research. 2017 Feb; 5(1): 1-4. doi: 10.1038/boneres.2016.56.

[18] Komolka K, Albrecht E, Schering L, Brenmoehl J, Hoeflich A, Maak S. Locus characterization and gene expression of bovine FNDC5: is the myokine irisin relevant in cattle? PloS One. 2014 Jan; 9(1): e88060. doi: 10.1371/journal.pone.0088060.

[19] Irving BA, Still CD, Argyropoulos G. Does IRISIN have a BRITE future as a therapeutic agent in humans? Current Obesity Reports. 2014 Jun; 3: 235-41. doi: 10.1007/s13679-014-0091-1.

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

[21] Park HS, Kim HC, Zhang D, Yeom H, Lim SK. The novel myokine irisin: clinical implications and potential role as a biomarker for sarcopenia in postmenopausal women. Endocrine. 2019 May; 64: 341-8. doi: 10.1007/s12020-018-1814-y.

[22] Elsen M, Raschke S, Sommerfeld M, Gassenhuber H, Eckel J. Comment on Wu and Spiegelman. Irisin ERKs the Fat. Diabetes. 2014 Sep; 63(9): e16. doi: 10.2337/db14-0776.

[23] Perakakis N, Triantafyllou GA, Fernández-Real JM, Huh JY, Park KH, Seufert J, *et al.* Physiology and role of irisin in glucose homeostasis. Nature Reviews Endocrinology. 2017 Jun; 13(6): 324-37. doi: 10.1038/nrendo.2016.221.

Ruan Q, Huang Y, Yang L, Ruan J, Gu W, Zhang X, Zhang Y, *et al.* The effects of both age and sex on irisin levels in paired plasma and cerebrospinal fluid in healthy humans. Peptides. 2019 Mar; 113: 41-51. doi: 10.1016/j.peptides.2019.01.004.

[25] Ruan Q, Zhang L, Ruan J, Zhang X, Chen J, Ma C, *et al.* Detection and quantitation of irisin in human cerebrospinal fluid by tandem mass spectrometry. Peptides. 2018 May; 103: 60-4. doi: 10.1016/j.peptides.2018.03.013.

[26] Polyzos SA, Anastasilakis AD, Efstathiadou ZA, Makras P, Perakakis N, Kountouras J, *et al.* Irisin in metabolic diseases. Endocrine. 2018 Feb; 59: 260-74. doi: 10.1007/s12020-017-1476-1.

[27] Liu JJ, Wong MD, Toy WC, Tan CS, Liu S, Ng XW, *et al.* Lower circulating irisin is associated with type 2 diabetes mellitus. Journal of Diabetes and its Complications. 2013 Jul; 27(4): 365-9. doi: 10.1016/j.jdiacomp.2013.03.002.

[28] Villarroya F. Irisin, turning up the heat. Cell Metabolism. 2012 Mar; 15(3): 277-8. doi: 10.1016/j.cmet.2012.02.010.

[29] Timmons JA, Baar K, Davidsen PK, Atherton PJ. Is irisin a human exercise gene? Nature. 2012 Aug; 488(7413): E9-10. doi: 10.1038/nature11364.

[30] Murao M, Imano T, Akiyama J, Kawakami T, Nakajima M. Effect of single bout downhill running on the serum irisin concentrations in rats. Growth Factors. 2019 Nov; 37(5-6): 257-62. doi: 10.1080/08977194.2020.1742118.

[31] Samy DM, Ismail CA, Nassra RA. Circulating irisin concentrations in rat models of thyroid dysfunction—effect of exercise. Metabolism. 2015 Jul; 64(7): 804-13. doi: 10.1016/j.metabol.2015.01.001.

Ozbay S, Ulupınar S, Şebin E, Altınkaynak K. Acute and chronic effects of aerobic exercise on serum irisin, adropin, and cholesterol levels in the winter season: Indoor training versus outdoor training. Chinese Journal of Physiology. 2020 Jan; 63(1): 21. doi: 10.4103/CJP.CJP_84_19.

[33] Seale P, Conroe HM, Estall J, Kajimura S, Frontini A, Ishibashi J, *et al.* Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. The Journal of Clinical Investigation. 2011 Jan; 121(1): 96-105. doi: 10.1172/JCI44271.

[34] Collins S, Yehuda-Shnaidman E, Wang H. Positive and

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DOI: https://doi.org/10.54393/pbmj.v6i07.905

negative control of Ucp1 gene transcription and the role of β-adrenergic signaling networks. International Journal of Obesity. 2010 Oct; 34(1): S28-33. doi: 10.1038/ijo.2010.180.

[35] Fernandez-Marcos PJ and Auwerx J. Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis. The American Journal of Clinical Nutrition. 2011 Apr; 93(4): 884S-90S. doi: 10.3945/ajcn.110.001917.

[36] Narkar VA, Downes M, Ruth TY, Embler E, Wang YX, Banayo E, *et al*. AMPK and PPARδ agonists are exercise mimetics. Cell. 2008 Aug; 134(3): 405-15. doi: 10.1016/j.cell.2008.06.051.

[37] Speakman JR. FTO effect on energy demand versus food intake. Nature. 2010 Apr; 464(7289): E1. doi: 10.1038/nature08807.

[38] Gesta S, Tseng YH, Kahn CR. Developmental origin of fat: tracking obesity to its source. Cell. 2007 Oct; 131(2): 242-56. doi: 10.1016/j.cell.2007.10.004.

[39] Park KW, Halperin DS, Tontonoz P. Before they were fat: adipocyte progenitors. Cell Metabolism. 2008 Dec; 8(6): 454-7. doi: 10.1016/j.cmet.2008.11.001.

Frühbeck G, Becerril S, Sáinz N, Garrastachu P, García-Velloso MJ. BAT: a new target for human obesity? Trends in Pharmacological Sciences. 2009 Aug; 30(8): 387-96. doi: 10.1016/j.tips.2009.05.003.

[41] Cinti S. Adipocyte differentiation and transdifferentiation: plasticity of the adipose organ. Journal of endocrinological investigation. 2002 Nov; 25: 823-35. doi: 10.1007/BF03344046.

[42] Cederberg A, Grønning LM, Ahrén B, Taskén K, Carlsson P, Enerbäck S. FOXC2 is a winged helix gene that counteracts obesity, hypertriglyceridemia, and diet-induced insulin resistance. Cell. 2001 Sep; 106(5): 563-73. doi: 10.1016/S0092-8674(01)00474-3.

[43] Feldmann HM, Golozoubova V, Cannon B, Nedergaard J. UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. Cell Metabolism. 2009 Feb; 9(2): 203-9. doi: 10.1016/j.cmet.2008.12.014.

[44] Barberá MJ, Schluter A, Pedraza N, Iglesias R, Villarroya F, Giralt M. Peroxisome proliferator-activated receptor α 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. Journal of Biological Chemistry. 2001 Jan; 276(2): 1486-93. doi: 10.1074/jbc.M006246200.

[45] Cao L, Choi EY, Liu X, Martin A, Wang C, Xu X, *et al*. White to brown fat phenotypic switch induced by genetic and environmental activation of a hypothalamic-adipocyte axis. Cell metabolism. 2011 Sep; 14(3): 324-38. doi: 10.1016/j.cmet.2011.06.020.

[46] Choi YK, Kim MK, Bae KH, Seo HA, Jeong JY, Lee WK, *et al*. Serum irisin levels in new-onset type 2 diabetes. Diabetes Research and Clinical Practice. 2013 Apr; 100(1): 96-101. doi: 10.1016/j.diabres.2013.01.007.

[47] Wen MS, Wang CY, Lin SL, Hung KC. Decrease in irisin in patients with chronic kidney disease. PloS One. 2013 May; 8(5): e64025. doi: 10.1371/journal.pone.0064025.

[48] Hondares E, Rosell M, Gonzalez FJ, Giralt M, Iglesias R, Villarroya F. Hepatic FGF21 expression is induced at birth via PPARα in response to milk intake and contributes to thermogenic activation of neonatal brown fat. Cell Metabolism. 2010 Mar; 11(3): 206-12. doi: 10.1016/j.cmet.2010.02.001.

[49] Li SW, Sun Y, Donelan W, Yu H, Scian J, Tang D, *et al*. Expression, purification, and characterization of recombinant human pancreatic duodenal homeobox-1 protein in Pichia pastoris. Protein Expression and Purification. 2010 Aug; 72(2): 157-61. doi: 10.1016/j.pep.2010.04.004.

[50] Fernyhough ME, Vierck JL, Hausman GJ, Mir PS, Okine EK, Dodson MV. Primary adipocyte culture: adipocyte purification methods may lead to a new understanding of adipose tissue growth and development. Cytotechnology. 2004 Oct; 46: 163-72. doi: 10.1007/s10616-005-2602-0.

[51] Miegueu P, Cianflone K, Richard D, St-Pierre DH. Motilin stimulates preadipocyte proliferation and differentiation and adipocyte lipid storage. American Journal of Physiology-Endocrinology and Metabolism. 2011 Nov; 301(5): E758-66. doi: 10.1152/ajpendo.00089.2011.

[52] Kahn BB and Jeffrey S. Flier obesity and insulin resistance. Journal of Clinical Investigations. 2000 Aug; 106(4): 473-81. doi: 10.1172/JCI10842.

[53] 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. International Journal of Obesity. 2016 Mar; 40(3): 443-51. doi: 10.1038/ijo.2015.199.

[54] Chen N, Li Q, Liu J, Jia S. Irisin, an exercise-induced myokine as a metabolic regulator: an updated narrative review. Diabetes/metabolism Research and Reviews. 2016 Jan; 32(1): 51-9. doi: 10.1002/dmrr.2660.

[55] Park MJ, Kim DI, Choi JH, Heo YR, Park SH. New role of irisin in hepatocytes: The protective effect of hepatic steatosis in vitro. Cellular Signalling. 2015 Sep; 27(9): 1831-9. doi: 10.1016/j.cellsig.2015.04.010.

[56] Zhang HJ, Zhang XF, Ma ZM, Pan LL, Chen Z, Han HW,

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DOI: https://doi.org/10.54393/pbmj.v6i07.905

et al. Irisin is inversely associated with intrahepatic triglyceride contents in obese adults. Journal of Hepatology. 2013 Sep; 59(3): 557-62. doi: 10.1016/j.jhep.2013.04.030.

[57] Calle EE and Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nature Reviews Cancer. 2004 Aug; 4(8): 579-91. doi: 10.1038/nrc1408.

[58] Lee CH, Woo YC, Wang Y, Yeung CY, Xu A, Lam KS. Obesity, adipokines and cancer: an update. Clinical Endocrinology. 2015 Aug; 83(2): 147-56. doi: 10.1111/cen.12667.

Shao L, Li H, Chen J, Song H, Zhang Y, Wu F, *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. 2017 Apr; 485(3): 598-605. doi: 10.1016/j.bbrc.2016.12.084.

[60] Zhang ZP, Zhang XF, Li H, Liu TJ, Zhao QP, Huang LH, *et al.* Serum irisin associates with breast cancer to spinal metastasis. Medicine. 2018 Apr; 97(17): e0524. doi: 10.1097/MD.0000000000010524.

[61] Hanahan D and Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan; 100(1): 57-70. doi: 10.1016/S0092-8674(00)81683-9.

[62] Gannon NP, Vaughan RA, Garcia-Smith R, Bisoffi M, Trujillo KA. Effects of the exercise-inducible myokine irisin on malignant and non-malignant breast epithelial cell behavior in vitro. International Journal of Cancer. 2015 Feb; 136(4): E197-202. doi: 10.1002/ijc.29142.

[63] Kong G, Jiang Y, Sun X, Cao Z, Zhang G, Zhao Z, *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. 2017 Nov; 38(5): 2647-56. doi: 10.3892/or.2017.5973.

[64] Liu J, Song N, Huang Y, Chen Y. Irisin inhibits pancreatic cancer cell growth via the AMPK-mTOR pathway. Scientific Reports. 2018 Oct; 8(1): 15247. doi: 10.1038/s41598-018-33229-w.

[65] Tekin S, Erden Y, Sandal S, Yilmaz B. Is irisin an anticarcinogenic peptide? Medicine Science. 2015 Dec; 4(2): 2172-80. doi: 10.5455/medscience.2014.03.8210.

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