



The role of a recently discovered peptide—irisin—in physiological and pathological processes

Review

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Abstract

Irisin, a cleaved fragment of fibronectin type III domain-containing protein 5 (FNDC5), was originally described as a factor stimulating browning of white adipose tissue, produced during physical exercise by skeletal muscles. However, irisin is not only a new and promising biomarker of metabolism; its expression has been found in a wide variety of tissues and organs such as the peripheral nerves, stomach, pancreas, and skin, and recent data also indicate its role in cancer. Numerous studies focus on the protective role of this protein, which could become an important factor in predicting disease risk, disease prognosis, or possible metastases in cancer patients. Possible use of irisin in therapy is also worth considering. The aim of this paper is to systematize knowledge on the role of irisin in patients and to draw attention to its role in skin diseases including acne vulgaris, psoriasis vulgaris, and hidradenitis suppurativa.

Keywords

adipose tissue • cancer • irisin • metabolism • skin

1. Irisin—the discovery and structure

Irisin was for the first time identified in 2012 by Bostrom et al. as a molecule secreted by exercise-induced skeletal muscles [1]. It is a 12kDa, peptide, a cleaved fragment of FNDC5 [1]. FNDC5, the irisin precursor, is a 20-32 kDa protein which gene *FNDC5* is encoded on chromosome 1 at position 35.1 (1p35.1) and its expression is controlled by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 α) in response to physical exercise. Originally, it was believed that the role of irisin is to transfer information between muscles and other tissues via cell surface receptors, hence the name of the discussed factor—irisin—the messenger of the Olympic gods. However, since the first research, the function of irisin has been the subject of many studies and seems to be multidirectional [2, 3]. Irisin is involved in physiological processes including energy metabolism and bone and muscle homeostasis, as well as pathological processes, i.e., carcinogenesis.

2. Tissue distribution

Initially, FNDC5 and irisin were reported in the context of expression of the latter on skeletal muscle cells, however, subsequent studies have shown that irisin is not only produced in skeletal muscles and transported by blood to target tissues, but it is also secreted in many other tissues [4]. High FNDC5 mRNA expression has also been demonstrated in smooth muscle cells of the rectum, cerebral arteries, and pericardium. Conversely, low expression has been observed in kidneys, liver, lungs, and fat cells [5]. An immunohistochemical study conducted by Aydin et al. found irisin in numerous tissues and organs, such as skeletal muscles, peripheral nerves, testes, pancreas, liver, spleen, and stomach [6]. Irisin was also found in plasma, saliva [7], and cerebrospinal fluid [8]. However, so far, there are no precise data or guidelines on how to determine its expression or units of measurement of its serum levels [9].

The most recent studies focus on discovering the receptor of irisin. In 2018, Kim et al. were the first to find that irisin binds to integrins of the αV class on the surface of adipocytes and osteoclasts [10]. This has been confirmed by demonstrating that irisin

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action is abolished due to a competitive inhibition of the $\alpha\beta 5$, $\alpha\beta 1$, and CD81 integrin complex on the adipocyte surface, which mediates the phosphorylation of focal adhesion kinase (FAK) pathway activated by irisin [11]. Bi et al. were the first to describe the effect of irisin on intestinal barrier repair, as it binds to $\alpha\beta 5$ integrins as its receptor and activates the AMP-activated protein kinase (AMPK-UCP 2) pathway, in reperfusion due to intestinal ischaemia [12]. Park et al. do not rule out existence of a different type of irisin receptor, but most studies confirm that irisin is a ligand for cell surface integrins [13]. Irisin has not been given an explicit function yet despite numerous studies.

3. The role of irisin in metabolism

A great interest in exercise-induced myokine secretion is aroused by its role in inducing browning of white adipose tissue (WAT), thereby increasing energy expenditure and improving metabolic profile of the body. White and brown adipose tissue adipocytes, originating from two different cell lines, have different functions in the body. In addition to their support functions, storing triglycerides during increased energy supply, cells of WAT are capable of producing adipokines that contribute to development of chronic inflammation and insulin resistance. This in turn leads to obesity, metabolic disorders, cardiovascular diseases, and even cancer [14, 15]. Brown adipose tissue (BAT) occurs in adults in small amounts and plays a role in the heat generation by way of non-shivering thermogenesis, as well as participating in prevention of obesity, diabetes, and other metabolic disorders [14, 15, 16, 17]. Accumulating data indicate the role of irisin in the browning of WAT cells and formation of a third type of adipose tissue, i.e., a beige adipose tissue ("*brite*"), small deposits between WAT adipocytes [18]. Beige adipose tissue cells show functional and molecular characteristics similar to BAT but not originating from the same cell lineage [18]. Under influence of stimuli— β -adrenergic stimulation or prolonged stimulation with PPAR α -agonist—these cells express and synthesise PGC-1 α and UCP1, proteins that were not present on WAT cells, had numerous mitochondria, and were capable of thermogenesis. The exact mechanism by which irisin affects WAT cells is not fully understood. It is known that this process is due in part to ability of irisin to increase the expression of mitochondrial uncoupling protein 1 (UCP 1), a regulator of thermogenic capability of brown fat, through phosphorylation of the p38 mitogen-activated protein kinase (p38 MAPK). Irisin-stimulated browning of WAT resulted in weight loss and improved glucose metabolism and is a promising finding primarily as a potential therapeutic agent for metabolic disorders.

Accumulating data indicate irisin is a factor protecting against diet-induced obesity [1]. Numerous studies on the relationship between irisin levels and degree of obesity, body mass index (BMI), glucose levels, insulin resistance, or other metabolic disorders resulting from obesity have been conducted, however,

their results are inconclusive, making work on a more thorough understanding of its function more intense [19, 20]. Vaughan et al. treated skeletal muscle cells with different irisin levels over 24 h and demonstrated its dose- and time-dependent effects on cell metabolism and increased mitochondrial uncoupling and stimulation of gene expression, i.e., peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), nuclear respiratory factor 1 (NRF1), mitochondrial transcription factor A (TFAM), glucose transporter 4 (GLUT4), and mitochondrial uncoupling protein 3 (UCP3) [21]. These results were similar to the ones obtained by Huh et al., who treated skeletal muscle fibres with irisin and observed increased expression of insulin-like growth factor 1 (IGF1) and reduced myostatin mRNA expression, which is essential for muscle cell growth. Furthermore, irisin was observed to inhibit differentiation of preadipocytes, while mature fat cells were reduced in size and contained less lipids. In addition, irisin stimulated expression of GLUT4, carnitine palmitoyltransferase 1A (CPT1a), PPAR α , and hormone-sensitive lipase (HSL), proteins essential for normal glucose and lipid metabolism and acting as glucose transporters [22]. Numerous studies have highlighted a positive correlation between serum irisin levels and obesity or excess weight in patients without established type 2 diabetes, probably to maintain a normal balance in glucose metabolism [23]. Serum irisin levels were lower in malnourished patients diagnosed with anorexia as compared to those with normal weight or obesity, who were found to have the highest levels of circulating protein [24]. Different irisin levels depending on degree of obesity are confirmed with a study which showed that diet-induced weight loss resulted in a 15% reduction in protein levels, while regaining baseline weight led to an increase of its levels. Some researchers have highlighted that irisin could be used as a predictive factor in assessing the risk of insulin resistance in patients who have not maintained their weight loss by diet. Half of the subjects were diagnosed with insulin resistance, highlighting the fact that baseline irisin levels were highest in these patients [25]. Irisin's versatile action and possible participation in various metabolic pathways in the human body should provoke in-depth studies, i.e., in patients with cardiovascular, renal, pulmonary or nervous system disorders, or metabolic bone diseases [26].

4. Role of irisin in carcinogenesis

Irisin secreted during regular exercise not only reduces inflammation, but also plays an important role in metabolic disorders. Obesity is associated with many cancers, both directly and indirectly (through release of pro-inflammatory adipokines, increased inflammation, or insulin resistance). Many studies focus on demonstrating the effect of irisin on carcinogenesis, but also on determining its prognostic or protective function and potential use in therapy. Previous studies on irisin in neoplastic cells have shown its expression in thyroid cancer, non-small cell lung

cancer, breast and ovarian, gastric, colorectal, and kidney cancer. Furthermore, elevated serum irisin levels were found in a number of cancers (breast, liver, colorectal, and kidney cancer). The effect of irisin on cancer cells has also been demonstrated *in vitro*. Its inhibitory effect on proliferation, growth, migration, and invasion of lung, breast, pancreatic, prostate and osteosarcoma cancer cells was confirmed by some authors [27, 28, 29, 30, 31, 32]. In contrast, other authors have reported opposite results in liver cancer, showing an irisin-mediated increase in proliferation, invasion, and migration by way of activation of the PI3K/AKT pathway [33]. Moon et al. demonstrated no effect of irisin on cancer cells of the endometrium, colon, thyroid, and oesophagus [34]. Due to a diverse expression of irisin in different types of cancer, some authors have suggested that its levels can be used for diagnostic purposes. For example, it has been demonstrated that malignant thyroid, lung, or kidney tumors and other tumor types could be differentiated from benign ones [35, 36] by investigating irisin expression. Its expression in lung cancer has been shown to be higher in adenocarcinoma than in basal cell carcinoma [37]. In contrast, studies of serum irisin levels in breast cancer patients have shown an inverse relationship between serum irisin levels and breast cancer risk [38]. The results of other studies indicate a role for irisin as a predictive factor. Exposure to various irisin levels sensitized neoplastic cells to the cytotoxic effect of doxorubicin in *in vitro* studies, in addition to inhibiting tumor cell proliferation [27]. Similar observations were reported by Liu et al. for pancreatic cancer cells, showing an increase in the percentage of cells undergoing apoptosis when exposed to irisin [29]. Opposite results were obtained by Shi et al., who showed a decreased cytotoxicity of the chemotherapeutic agent on liver cancer cells [33].

The above observations suggest that irisin could become a new marker in diagnosis and differentiation of cancer. There are even publications suggesting the possible use of irisin as an anti-tumor agent, however, divergent data indicate the need for further in-depth research [39, 40].

5. Irisin in skin diseases

As a protein with an ambiguous role, irisin is still being extensively studied. There are only four papers in dermatology to date about the role of irisin in skin disorders, including: psoriasis, hidradenitis suppurativa, acne vulgaris, and acanthosis nigricans. Interestingly, despite extensive research on irisin expression in solid tumors, the assessment of irisin expression in skin cancer, being the most common cancer, is yet unexplored [41].

Psoriasis has been treated not only as a skin disorder, but as a systemic disease, for some time now. Patients diagnosed with psoriasis are at higher risk of metabolic disorders and cardiovascular incidents. At the same time, in many cases it is obesity that predisposes to psoriatic skin manifestations. Inflammatory mediators produced by adipocytes trigger a cascade of

pathological processes in the skin and psoriatic lesions develop when certain environmental factors and genetic predisposition are present [42, 43]. A study on 37 patients with active plaque psoriasis conducted in 2017 by Baran et al. examined a possible correlation between serum irisin and Psoriasis Area and Severity Index (PASI), Body Mass Index (BMI), inflammatory and biochemical blood parameters, lipid profile, and efficacy of topical therapy. Comparison of serum irisin levels between patients and controls showed no statistically significant correlation, although protein levels were higher in the former group. Similarly, severity of the disease (as measured with PASI), degree of obesity, liver enzyme activity, glucose levels, and lipid metabolism had no effect on irisin levels. On the other hand, it positively correlated with patients' age, disease duration, and inflammatory markers (CRP and ESR). Topical therapy used (5% salicylic acid and 0.3% dextran, for 2 weeks) showed no effect on median level of the protein studied [44].

Hidradenitis suppurativa (HS) is another skin disease that is often concomitant with systemic diseases [45], including obesity, diabetes, metabolic syndrome, or other inflammatory diseases [46]. This chronic and recurrent dermatosis affects hair follicles and manifests with painful inflammatory nodules, abscesses, and fistulas, with lesions resolving with scarring. Özkur et al. were the first to assess serum irisin levels with patients with HS in correlation with obesity or other metabolic parameters. They did not show any significant differences in mean irisin levels between patients and the control group. Considering that subjects with healthy BMIs were enrolled accordingly to the control group, a positive correlation between BMI and irisin was only noted in this group. Waist circumference was significantly higher in patients, but its value correlated positively with irisin levels regardless of the group [47]. Another study [48] demonstrated a decrease in serum irisin levels in patients undergoing a restrictive diet resulting in reduced body weight. Subsequent weight gain resulted in an increase in irisin levels.

Insulin resistance is one of aetiological factors of acne vulgaris. Mustafa and El-Shimi have demonstrated a relationship between insulin resistance and severity of acne lesions. They have also shown that irisin may be treated as a prognostic factor of this dermatosis, proving a negative correlation between its serum levels, HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) and acne flare-ups [49].

Many studies have demonstrated the relationship between irisin, hyperinsulinaemia, and obesity. Acanthosis nigricans (AN) is one of the manifestations of insulin resistance, manifested by skin hyperpigmentation and hyperkeratosis [50]. Only one article has been published so far explaining the relationship between irisin and acanthosis nigricans associated with obesity. Chen et al. conducted a study in which they demonstrated that irisin levels were significantly higher in obese subjects. Its levels positively correlated, among other factors, with BMI, waist cir-

cumference, and lipid metabolism. When the group with obesity (with no difference in BMI) was divided into patients with acanthosis nigricans and patients without acanthosis nigricans, the study showed that serum irisin levels were higher in the former subgroup, which may suggest a relationship between acanthosis nigricans and obesity. The same subgroup (obese patients with acanthosis nigricans) showed better glucose tolerance, which may be attributed to the protective role of irisin [51].

6. Summary

In conclusion, irisin is one of the most recently discovered peptides, and its role in physiological and pathological processes is an interesting research subject. Its wide occurrence in various tissues and organs gives us a number of new possibilities. There are promising discoveries of the use of this protein as a prognostic factor in many diseases, including cancer, or as a predictive factor in metabolic disorders and cancer, however, further research is required to fully establish the potential role of irisin.

Abbreviations

AN - acanthosis nigricans, **BAT** - brown adipose tissue, **BMI** - Body Mass Index, **CPT1a** - carnitine palmitoyltransferase 1A, **FNDc5** - fibronectin type III domain-containing protein 5, **GLUT4** - glucose transporter type 4, **HS** - hidradenitis suppurativa, **HSL** - hormonsensitive lipase, **IGF1** - insulin-like growth

factor 1, **NRF1** - nuclear respiratory factor 1, **p38 MAPK** - p38 mitogen-activated protein kinase, **PASI** - Psoriasis Area and Severity Index, **PGC-1α** - peroxisome proliferator-activated receptor γ coactivator-1 alpha, **PPARα** - peroxisome proliferator-activated receptor-α, **TFAM** - mitochondrial transcription factor A, **UCP1α** - mitochondrial membrane uncoupling protein 1 alpha, **UCP3** - mitochondrial uncoupling protein 3, **WAT** - white adipose tissue.

Authors' Contribution

M.B.O.: writing - original draft preparation; literature review;
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Conflict of Interest

The authors have no potential conflicts of interest to declare.

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