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A new member of the myokine family: Irisin

Cigdem Tekin[1], Suat Tekin[2], Suleyman Sandal[2]

[1]Inonu University, Faculty of Medicine, Department of Public Health, Malatya, Turkey
[2]Inonu University, Faculty of Medicine, Department of Physiology, Malatya, Turkey

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Abstract
Skeletal muscle is an important tissue which functions as an endocrine organ and secretes the factors called myokine. Irisin is a thermogenic peptide which has been recently defined as a new myokine. The physiological roles of these peptides have been revealed in recent studies. The purpose of this review is to explain the known physiological roles of irisin.

Keywords: Irisin, myokine, endocrine system, energy metabolism, physiological roles

Introduction

Skeletal muscle has recently been described as a new endocrine organ. The cytokines and other peptides produced by skeletal muscle are secreted from the muscle fibers. These factors secreted from skeletal muscle are classified as a myokine. These myokines which are secreted from the myocytes and are brought into circulation in response to muscle contraction have autocrine, paracrine and endocrine effects [1]. Irisin was defined as a new member of the myokine family by Bostrom et al. in 2012. It has been suggested that irisin secreted during skeletal muscle contraction can mediate some metabolic processes [2]. For a long time, the researchers have advocated the idea that the exercise factors secreted during skeletal muscle contraction can regulate some of the metabolic changes associated with exercise [1,3]. It was reported that irisin can be evaluated as an anticancerogenic peptide for the early detection and prevention of cancer in addition to its effects on metabolism [4, 5]. The purpose of this review is to contribute to a better understanding of the possible physiological roles of irisin.

The History of Irisin

The existence of irisin has been revealed by Bostrom et al. in 2012 in the study called the "A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis". Because irisin transmits a signal to other tissue from muscle tissue, its name originates from the Iris that is the Ancient Greek goddess is believed to give people happy news according to Greek mythology [2].

***Corresponding Author:** Suleyman Sandal, Inonu University, Faculty of Medicine, Department of Physiology, Malatya, Turkey
E-mail: suleyman.sandal@inonu.edu.tr

The Biochemical Structure of Irisin

Irisin occurs as a result of that fibronectin type III domain-containing protein 5 (FNDC5) consisting of 206 amino acids loses 94 amino acids in skeletal muscle during exercise [2]. The enzyme that cleaves the FNDC5 protein for the formation of irisin is not yet known.

Irisin consists of 112 amino acids and is a 12-kDa peptide hormone [2]. The recombinant forms of irisin with different numbers of amino acids (39, 49, 53, 70 and 112 amino acids) are commercially available. However, it is not known which form is more biologically active and whether the forms have different physiological roles.

It has been revealed in the studies conducted between the species that the structures of irisin showed great similarity. For example, irisin protein in the plasma of human and mouse (*Mus musculus*) was found to be similar (100%) and also this similarity was determined to be at high levels in other organisms [2].

The Irisin Receptor

Although the number of studies is steadily increasing to explain the roles of irisin, the irisin receptor that mediates, these roles are still unknown. In the first study conducted to determine the irisin receptor, it has been suggested that irisin performs its effects through a cell surface receptor [2]. In another study, it has been shown that irisin dimers may be important for ligand-receptor interaction [6]. The discovery of the tissues where irisin receptor or receptors are present would contribute significantly to the understanding of the physiological importance of irisin.

The Localization of Irisin in Tissues

In a study conducted on humans, it has been shown that the irisin precursor FNDC5 is found in 47 different tissues, particularly tissues such as the muscle, pericardium, rectum and brain [7]. The first information about irisin is that it is secreted from muscle tissue during exercise. However, it has been revealed in many subsequent studies that the peptide is synthesized in many tissues other than muscle tissue. Studies have shown that irisin is found in the subcutaneous adipose tissue, brain, heart muscle, testis, lung, spleen, stomach, pancreas, human breast milk, saliva, cerebellar Purkinje cells, and CSF [8-10]. Moreover, it was reported that irisin is found in hepatocytes by the flow cytometry and cell imaging techniques [11]. The expression of irisin in various tissues indicates that further studies are needed to confirm the important physiological roles and other functions of this peptide.

The Synthesis and Secretion of Irisin

Peroxisome proliferator-activated receptor gamma (PPARγ) and PPARγ coactivator 1 alpha (PGC1-α) which are stimulated by exercise and cause energy expenditure mediate the increase in FNDC5 gene expression. PGC1-α is a mediator in the programming of energy metabolism, and also it controls the oxidative metabolism by mitochondrial biogenesis in many cell types [12, 13]. There are five different proteins synthesized and secreted by the muscle tissue via PGC1-α: FNDC5, interleukin-15 (IL-15), Vascular endothelial growth factor beta (VEGFβ), Leucine-rich alpha-2-glycoprotein 1 (Lrg1), and Tissue inhibitor of metalloproteinase-4 (TIMP-4) [14]. Studies report that the transmembrane protein FNDC5 is larger than the cellular protein FNDC5 [2, 15]. This situation has led researchers to question whether a part of the protein is secreted or not. Researchers who take this structure into account put forward a new hypothesis that FNDC5 is synthesized as type I membrane protein and is proteolytically cleaved and then the amino-terminal (N) end of the protein is released into the extracellular environment. As a result of studies conducted in accordance with this assumption, it has been revealed that FNDC5 (also known as FRCP2 and PeP) is released from skeletal muscle during exercise via PGC1-α and irisin occurs with cleavage of this protein by an unknown protease.

In a study, it has been revealed that the formation of irisin (cleavage and release) is similar to transmembrane polypeptides such as epidermal growth factor and alpha-converting growth factor [2].

The Relationship of Irisin with Exercise

In the study of Bostrom et al. who discovered irisin, they stated that different irisin fragments are present in the plasma of human and mouse and that the changes in skeletal muscle FNDC5 gene expression have an effect on the levels of these structures. It was reported in the study that circulating irisin level was also increased after a while in parallel with the increase in FNDC5 expression level in skeletal muscle after exercise [2].

Some studies conducted on humans support Bostrom et al. For example, Kraemer et al. stated that circulating irisin level was temporarily increased within the first few hours after exercise [16]. In another study, it has been shown that circulating irisin level was increased by about 20% after acute exercise [7]. In these studies where the researchers consider FNDC5 and irisin expression levels, they reported that acute exercise significantly affected circulating irisin level compared to chronic exercise. However, several other studies have emphasized that circulating irisin level did not change after either acute or chronic exercise [17, 18]. Hecksteden et al. reported that circulating irisin level was not significantly affected after either strength-based or normal chronic exercise [19]. In another study, it was reported that although PGC1-α and FNDC5 gene expression was increased after chronic exercise, circulating irisin level was decreased [20]. In the past studies, the different analysis methods (such as ELISA and Western Blot) for determining irisin level may also lead to a different assessment of possible outcomes. As it is illuminated that this newly defined peptide interacts with which physiological and molecular pathways, the information about the regulation of this peptide would be certain.

The Relationship of Irisin with Central Nervous System

It is thought that FNDC5 and irisin might have a number of roles in the central nervous system besides signal transmission between skeletal muscle and adipose tissue. Although the effect of PGC1-α on FNDC5 is clarified by the studies performed, for instance, the primary physiological functions of these molecules are not clear in important tissues such as the brain [21-23]. In a study, it has been shown that irisin is found in rat and mouse cerebellar Purkinje cells [8]. Moreover, the same researchers put forward a new hypothesis that “irisin, produced in the cerebellum, may be a regulator of adipocyte metabolism with many synapses in the spinal cord” and they stated that this hypothesis needs to be confirmed [8]. Hashemi et al. found that FNDC5 is necessary to achieve adequate nerve differentiation in mouse embryonic stem cells [24]. In the same study, the researchers determined that FNDC5 was decreased in mouse embryonic stem cells during both neuronal progenitor formation and their differentiation [24]. In another study, it was stated that hippocampal neurogenesis is regulated in a dose-dependent manner by irisin [25]. While the physiological concentrations (5-10 nmol/L) of irisin did not have any influence on proliferation of mouse H19-7 hippocampal neuronal cells, the pharmacological concentrations (50-100 nmol/L) increased the level of proliferation [25]. All these evidence show that irisin can play a central role. In this regard, irisin may mediate the effect of exercise on hippocampal neurogenesis which is mainly affected by Alzheimer's disease [26, 27]. It is thought that irisin may also mediate positive effects of exercise on Parkinson's and some other neurodegenerative diseases [28-30]. In addition, irisin, a thermoregulatory peptide, can play an active role in this process by stimulating the hypothalamus related fields in the central control of body temperature. It was reported that central administration of irisin increased body temperature in rats [31, 32].

There are very few studies that indicate the effects of irisin on central nervous system. Future studies would be effective in determining that irisin plays which roles or mediates which physiological and molecular processes in the central nervous system.

The Relationship of Irisin with Metabolism

Irisin is a thermogenic protein that promotes energy use by providing the transformation of white fat into brown fat. The most important physiological role of this hormone is to provide the development of brown fat tissue from white fat tissue [33]. Irisin performs this development by increasing the levels of other browning proteins, especially UCP1. Consequently, the amount of white fat tissue called energy store is reduced and so the stored energy is released. With the discovery of irisin, it is a hormone that attracts the attention of researchers, and also it is anticipated as hope in the treatment of many metabolic disorders, including obesity and type 2 diabetes in the future [34-36]. Few studies investigated the relationship between reduced serum irisin level and insulin resistance or diabetes. The researchers reported that irisin level was lower in type 2 diabetic patients [37-39], and also irisin level showed a negative correlation with fasting glucose level [36] and HbA1c [36,39]. These results suggest that irisin level may be affected by the development of insulin resistance. Yuksel et al. reported that irisin level in maternal and cord blood was lower in patients with gestational diabetes mellitus compared to controls [40]. It was reported in another study conducted in patients with gestational diabetes mellitus that CSF irisin level was significantly higher [41]. Crujeiras et al. have emphasized that irisin may play an active role in controlling insulin sensitivity [42].

Moreover, it is among other research topics that what type of contribution irisin has on the known benefits of exercise on health. Brailoiu et al. reported that the exogenous administration of irisin into cultured nucleus ambiguous neurons activated these nerve cells and caused an increase in cytosolic Ca^{2+} concentration and triggered neuronal depolarization. These neurons are responsible for vagal impulses, which are projected on the heart and are an important regulator of heartbeat in the living system. Moreover, in vivo experiments, it has been shown that bradycardia developed in rats after microinjection of irisin [43]. In another study, it has been found that central administration of irisin increased blood pressure and heart contraction. However, researchers have determined that peripheral administration of irisin reduced blood pressure in both control and spontaneously hypertensive rats [44]. These results show that central and peripheral administration of irisin exhibit different effects.

It is reported that irisin has significant effects on the hypothalamus-pituitary axis accepted as the central regulator of the endocrine system. Researchers reported that serum thyroid hormone levels were decreased after central administration of irisin [45]. Irisin is also a peptide responsible for food intake and nutritional behavior. It was reported that long-term central administration of irisin stimulated nutrient uptake [32] and reduced serum leptin level and increased serum ghrelin level [46]. In a study performed in obese Chinese men, Zhang et al. showed that there was a negative correlation between serum irisin concentration and liver triglyceride level [47]. In a study conducted in obese and non-obese women and men, it was reported that irisin level was higher in obese than non-obese and in men than women [48]. In another study, it was reported that circulating irisin levels were higher in morbidly obese individuals compared to normal weight and anorexic patients [49]. In the study of Moreno et al., they have suggested that there was an opposing relationship between irisin level and obesity and a decrease in circulating irisin level may cause lubrication in the waist and hips and this may result in obesity [50].

Moreover, it has been reported that irisin may have effects on reproductive behavior. It has been reported that irisin caused a decrease in hypothalamic GnRH levels and reduced serum LH, FSH and testosterone levels [51].

FNDC5 regulates the expression of the genes including UCP1, Elov13, Cox7a and OTOP1, which provide browning [2,52]. For example, 20 nM FNDC5 which was added to adipose tissue culture increased UCP1 gene expression about 7 times [2]. In another study, it was shown that exogenous administration of irisin caused an increase in the expression of fat tissue UCP1 and muscle tissue UCP3 [53]. Increased UCP1 expression prevents ATP synthesis and also causes energy expenditure by leading to heat formation [54]. All these results show that FNDC5 regulates thermogenesis activation in white adipose tissue.

Result

Skeletal muscle is not only one of the elements of the movement system but also functions as an endocrine organ. Moreover, skeletal muscle produces many myokines and releases them into circulation. Irisin that has recently participated in these myokines regulates energy metabolism, cardiovascular functions, insulin sensitivity, and vascular responses. However, it is not clear that how it performs these regulations via which receptor/receptors. As a result, it is appears that irisin is to be an important moderator in the realization of many physiological processes. But, the available literature on physiological roles of irisin is limited. Therefore, it is necessary to increase the number of studies to clarify the physiological mechanisms.

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