

To Explore the Research Progress of Irisin As a Therapeutic Drug for Diseases Based on Sequence Conservation

Junyu Chen¹, Lijun Guo¹, Peng Peng¹, Jiaming Wu¹, Huaidong Zhang^{1,2}, Feng Liu^{1,2}, Qin Li^{1,2*}

¹ College of Life Sciences, Fujian Normal University, Fuzhou, China

² Engineering Research Center of Industrial Microbiology, Ministry of Education, Fuzhou, Fujian, China

Email Address

liqin@fjnu.edu.cn (Qin Li)

*Correspondence: liqin@fjnu.edu.cn

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Abstract:

Irisin, a myokine discovered in 2012, has attracted extensive research due to its ability to induce browning of adipocytes and improve metabolic function. The potential therapeutic applications of this exercise-induced hormone are being explored. Irisin exists in many different species of animals, and its sequence has a high degree of cross-species conservation, which has the potential to be developed as a biological drug. Existing studies have found that the level of irisin in patients with neurological and metabolic diseases is significantly different from that in healthy people. Therefore, irisin is considered to have therapeutic effects on the dysfunctions of the nervous system and endocrine system, and the underlying molecular mechanisms have been continuously explored. In this review, we discuss the sequence conservation of irisin sequence among multiple species, combined with the discovery and research progress of irisin in related diseases, and discuss the possibility of irisin as a therapeutic drug for related diseases.

Keywords:

Irisin, FNDC5, Disease, Conservation of Sequence

1. Introduction

Irisin is a myokine composed of 112 amino acids that is secreted mainly in response to exercise stimulation. In 2012, The researchers found that human peroxisome proliferator-activated receptor- γ coactivator-1 α , PGC-1 α can promote the secretion of fibronectin type III domain-containing protein 5 (FNDC5), a precursor of Irisin [1]. FNDC5, a member of the fibronectin family of extracellular matrix proteins, plays a role in neuronal development, and its expression in brain tissue has specific functions [2]. After proteolytic cleavage, FNDC5 produces the hormone Irisin [1].

Irisin exists in many animals and is highly conserved [3]. Previous studies have shown that irisin secretion is up-regulated after exercise, especially in skeletal muscle

tissue [4]. In addition, Irisin has been shown to regulate thermogenesis by inducing browning of human white adipose tissue [5]. Therefore, iris is a promising therapeutic agent for the treatment of diseases. Irisin can regulate a variety of physiological systems, including metabolic system, nervous system and motor function, which may be related to related factors such as Irisin's precursor protein FNDC5 and PGC-1 α [6].

This article will review the effects of Irisin on diseases and the current research progress, and discuss the possible contribution of Irisin in the treatment of diseases combined with the sequence changes of Irisin in different species.

2. Discussion on the Sequence of Irisin

2.1. Controversy about Irisin sequence

The muscle factor Irisin is hydrolyzed from its precursor, FNDC5. The composition of human FNDC5 consists of a 31-amino acid signal peptide at the N terminal, a fibronectin type III domain, a binding domain, a transmembrane domain and a C-terminal hydrophobic domain. Notably, the signal peptide length of human FNDC5 is different from that of the homologous gene of other species, which contains a 28 amino acid signal peptide [7].

The source of uncertainty is the high evolutionary conservation of FNDC5 precursors across species, and the human FNDC5 initiation codon mutates from ATG to ATA [8]. Proteins that initiate translation on ATA codons are extremely rare in humans [9,10]. Comparative analysis showed that ATG was the starting codon of non-human anthropoid ancestors, while the shift to ATA occurred only in hominid evolution, suggesting a selective advantage for reduced expression of FNDC5 [11]. Consistent with this premise, early irisin detection work only found low levels of irisin in human tissues [12]. However, tandem mass spectrometry was able to quantitatively analyze Irisin in human blood, showing that FNDC5 can indeed be translated and processed into Irisin by proteolysis despite the ATA initiation codon [13]. In addition, the existence of Irisin in human cerebrospinal fluid was confirmed and quantified by tandem mass spectrometry, which further verified the expression of FNDC5 in human body and the biosynthesis of Irisin [14]. Follow-up analysis of cerebrospinal fluid Irisin levels of different ages and genders showed that healthy men had slightly higher Irisin concentrations than women [15]. Together, these findings provide strong evidence for the expression of Irisin in humans and establish quantitative methods for future studies of this muscle factor.

Despite the apparent regulatory role of Irisin, its receptor remains unclear. It was initially found that irisin induces glycolysis in adipocytes through glucose transporter type 4 (GLUT4) and inhibits gluconeogenesis in hepatocytes, suggesting that hepatocytes are candidate targets for Irisin [16,17]. Integrin β 1 was identified as a potential irisin receptor by cross-linking mass spectrometry. Subsequent experiments showed that integrin α V β 5 inhibitors could block the irisin signaling pathway, suggesting that α V β 5 is a high confidence Irisin receptor. Other studies have suggested that α V β 5 may form irisin signal transducers in the complex with α V β 1 and transmembrane protein CD81 [18,19]. Validation experiments using α V β 5 blocking antibodies confirmed the weakened activity of Irisin, further supporting α V β 5 as the main functional receptor of Irisin [20].

2.2. Multi-species comparison of Irisin sequences

Irisin is highly sequentially conserved among different species. Studies have shown that Irisin is widely distributed among multiple animal species and is also conserved in terms of protein function [21]. Multiple sequence alignments showed that the entire irisin sequence (positions 1-112) was highly conserved across species. In addition, a high degree of sequence conservation was observed in the C-terminal region of the FNDC5 precursor (positions 113-181), suggesting that in addition to Irisin, the sequence encoding the FNDC5 protein also exhibits evolutionary conservation (Figure 1). Bioinformatic analysis showed that Irisin and its precursor protein FNDC5 showed a large number of conserved sequences during evolution.

The conserved nature of proteins can reveal the regions in which proteins have unique functions, and has great significance and implications in the biomedical analysis of proteins. The conserved region of a protein is often a unique functional group or domain, which may be a target region with binding ability and can be used as a site for protein development and optimization, and is of great value in the development of protein drugs [22,23]. Therefore, for Irisin with conservative sequence, it may have the potential to be developed as a disease treatment drug.

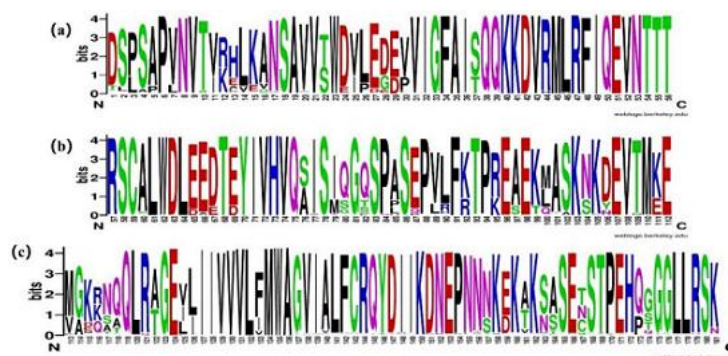


Figure 1. (a) cross-species sequence alignment of irisin /FNDC5, residues 1-56; (b) cross-species alignment of irisin /FNDC5, residues 57-112; (c) cross-species sequence alignment of irisin /FNDC5, residues 113-181.

3. Diseases for Which Irisin May Have Therapeutic Effects

3.1. Metabolic diseases

Since its discovery, the major role of Irisin is thought to be to stimulate the browning of human white adipose tissue (WAT), leading to the formation of brown adipose tissue (BAT). In the human body, white adipose tissue is responsible for energy storage, while brown adipose tissue consumes energy through thermogenesis [24]. Indeed, the pathway by which Irisin stimulates fat browning has been elucidated through p38 and ERK signaling pathways and has been suggested to have the potential to treat metabolic diseases related to energy expenditure [25]. However, irisin may not act on short-term energy expenditure, but is associated with energy expenditure over a long period of time [26]. Meanwhile, studies have found that Irisin levels can regulate high energy expenditure, which is a feasible therapeutic target for the treatment of obesity [27]. In addition, Irisin has been shown to ameliorate obesity symptoms by altering macrophage polarization in mouse models [28].

Type 2 diabetes mellitus (T2DM) is another disease for which Irisin may have potential therapeutic effects. T2DM includes a spectrum of metabolic dysfunctions in

which insulin resistance leads to dysregulation of glucose homeostasis. T2DM often coexists with obesity, because fat hypertrophy in obese patients is the main cause of insulin insensitivity [29]. Since its discovery, Irisin has been suggested to regulate glucose metabolism. It has been confirmed that circulating Irisin levels are reduced in patients with T2DM compared with healthy controls [30]. This phenomenon has also been observed between normoglycemic individuals and patients with nonalcoholic fatty liver disease [31,32]. In addition, comparisons between patients with T2DM and those with normal glucose tolerance further suggest that Irisin plays a role in the pathogenesis of diseases characterized by impaired glucose control [33]. As for the relationship between irisin and glucose metabolism, some studies have found that irisin and β -Arrestin-2 regulate glucose metabolism in T2DM patients by inhibiting the p38 signaling pathway to reduce glucose uptake [34]. At present, Irisin has been found to inhibit oxidative/nitrifying stress by inhibiting PKC- β /NADPH oxidase and NF- κ B/iNOS signaling cascade, thus causing therapeutic effects and thereby reducing vascular endothelial dysfunction in T2DM patients [35].

3.2. Neurological diseases

Initially, Irisin was thought to be a muscle factor induced primarily by physical exercise. However, with the deepening of research, Irisin is expressed in different tissues of the whole body, including skeletal muscle cells, cardiomyocytes and nerve cells [36]. Subsequent studies revealed the presence of Irisin in the cerebro-spinal fluid (CSF) and demonstrated its ability to cross the blood brain barrier (BBB), suggesting that Irisin may enter the central nervous system, It regulates Alzheimer's disease (AD) and other nervous system diseases [37].

AD is a neurodegenerative disease with clinical manifestations of dementia and memory impairment, and pathological manifestations are the accumulation of amyloid plaques and neurofibrillary tangles in the brain. AD leads to metabolic dysregulation, cardiovascular disease, and the risk of death [37]. Previous studies have suggested that Irisin may play a regulatory role in the pathogenesis of AD. Therefore, various studies have been carried out to investigate the mechanism behind this phenomenon [38]. Studies have shown that Irisin can activate STAT3, a signaling cascade capable of stimulating hippocampal neurogenesis and promoting cell proliferation, suggesting that irisin may directly stimulate nerve cell growth [39,40]. Mouse knockout models have shown that the precursor protein of Irisin, FNDC5, affects the maturation of neurons and astrocytes, and the loss of FNDC5 leads to reduced differentiation of neural progenitor cells [41]. Other groups have found evidence for a potential feedback regulatory loop between FNDC5 and PGC-1 α , with PGC-1 α stimulating the secretion of FNDC5 and brain-derived neurotrophic factor (BDNF), which is induced by exercise. BDNF is essential for hippocampal neurogenesis and synaptic plasticity [42]. Studies have shown that the symptoms of AD patients can be improved by regulating BDNF [43]. FNDC5 may regulate hippocampal neurons by acting on BDNF. Although the exact mechanism needs to be further elucidated, this represents that the pathway of Irisin acting on BDNF may be a potential therapeutic pathway to improve memory deficits in Alzheimer's disease [44].

4. Mechanism of Action of Irisin

4.1. Molecular mechanisms of Irisin in metabolic system diseases

Although many studies have revealed the beneficial biological functions of myokine Irisin, the study of the related signaling pathways and the molecular mechanisms underlying the regulation of Irisin metabolism is still an active area of research.

Irisin plays a role in fat browning by stimulating p38 mitogen-activated protein kinase (MAPK) and extracellular regulated protein kinases (ERK1/2). ERK, a key mediator of cell signaling. Treatment with recombinant irisin resulted in robust phosphorylation of p38 and ERK, as well as a significant upregulation of the browning related gene UCP1 [25]. There is another mechanism by which Irisin regulates glucose homeostasis: irisin significantly enhances cellular glucose uptake both in vivo and in vitro by activating MAPK signaling [8,45]. This finding elucidates the pathway by which Irisin improves systemic glucose regulation. In addition, irisin can inhibit body fat accumulation by interacting with adipose triglyceride lipase (ATGL) and fatty acid synthase (FAS) [46]. Irisin controls the metabolic rate by controlling body fat size, which is also considered to be the main way that Irisin affects the metabolic system and achieves therapeutic relevance for related metabolic diseases.

These data suggest that irisin enhances insulin sensitivity and glucose tolerance through MAPK-dependent regulation of glucose transport, as well as the manner in which it improves body fat metabolism, which is the main way in which Irisin affects metabolic diseases.

4.2. Molecular mechanisms of Irisin in nervous system diseases

Patients with neurological diseases are often accompanied by metabolic diseases [47]. Although the mechanism is still unclear, many hypotheses have been proposed. For example, polyunsaturated fatty acids, which are involved in the neuroinflammation of AD, affect the function of the BBB, leading to the transport of related lipids through the BBB and further affecting the cognitive ability of the brain [48,49]. Metabolic diseases are related to neurological diseases [50].

On the other hand, experiments on the AMPK signaling pathway of irisin have shown that Irisin can reduce cellular inflammation through the AMPK signaling pathway, which is a possible mechanism by which irisin reduces nervous system inflammation in AD diseases, and Irisin may achieve the therapeutic effect on nervous system diseases in this way [49,50].

Combined with the finding of abnormal levels of Irisin in patients with nervous system diseases and the function of Irisin in metabolic regulation, as well as the mechanism of Irisin in the treatment of nervous system related diseases, Irisin may have therapeutic potential in some nervous system diseases.

5. Conclusions

Studies on Irisin have proved that Irisin can be used as a way to treat diseases. Irisin mainly plays a role in metabolic regulation in the human body. Significant differences have been found in the level of Irisin in patients with metabolic diseases and that in normal patients, and relevant pathways have also been found. However, how to apply Irisin to clinical treatment is still a problem to be studied.

Irisin has been proved to be a highly conserved protein that exists across multiple species, but how to combine the conserved nature of Irisin with the functional nature

of Irisin and apply it to disease treatment remains to be studied. Based on the conservation of Irisin sequence, the presence of Irisin in other species will have great development value. At the same time, the sequence conservation of Irisin also suggests that Irisin has the potential as a biological drug.

The ability of Irisin to have a therapeutic effect on related diseases has also been extensively studied. For example, the level of Irisin in patients with T2DM or AD is significantly abnormal from that in normal patients, and relevant mechanism studies also suggest that Irisin plays a regulatory role in some functional abnormalities through signaling pathways such as MAPK. This suggests that Irisin may have potential as a drug for related diseases.

Irisin, as a newly discovered muscle factor hormone in the 21st century, has shown great potential in disease treatment. The sequence conservation of Irisin proves that Irisin has the development value in biomedicine. Studies on the levels of Irisin in patients with related diseases also indicate that Irisin can be used as a target for related diseases. Although the specific mechanism of Irisin remains to be further elucidated, the huge role of Irisin in the clinical medical field deserves further research and development.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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