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Irisin – A Multifunctional Myokine with Therapeutic Potential in Metabolic, Cardiovascular, Neurodegenerative, and Musculoskeletal Diseases

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ABSTRACT

The problem of metabolic, cardiovascular, neurodegenerative, and musculoskeletal diseases is incredibly significant these days due to their high occurrence rate among people globally. Irisin is one of the myokines that has become relevant for multiple physiological roles and has therapeutic potential in different diseases. It increases thermogenesis and improves glucose metabolism by converting white into beige fat tissue. Patients with obesity and type 2 diabetes demonstrate decreased levels of irisin, suggesting a connection to insulin resistance and metabolic dysfunction. Irisin shows promising therapeutic properties for diabetes complications due to its protective effects on vascular endothelial cells and kidney function. Additionally, this myokine is vital in neurological conditions, such as Alzheimer's disease (AD), by reducing amyloid-β accumulation, supporting synaptic plasticity, and limiting oxidative stress and inflammation. In the cardiovascular system, irisin protects the heart muscle by improving mitochondrial function, reducing infarct size, and regulating the activity of the vagus nerve. Scientists proved that irisin is important for the musculoskeletal system by stimulating muscle growth and regeneration, preventing atrophy, and supporting bone remodeling via osteoblast activation and osteoclast differentiation. In this review, we discuss the role of irisin as a myokine with significant therapeutic potential in metabolic, neurodegenerative, cardiovascular, and musculoskeletal disorders.

Key words: irisin, type 2 diabetes, cardiovascular, neurodegenerative, musculoskeletal

1. INTRODUCTION

Irisin is a myokine produced during physical activity from fibronectin type III domain-containing protein 5 (FNDC5), which is expressed in skeletal muscle, heart, adipose tissue, and liver (Boström et al., 2012). One of the most important functions is the ability to stimulate the conversion of white adipose tissue into beige fat. This process enhances thermogenesis and improves glucose regulation, leading to a better metabolic balance (Boström et al., 2012; Lee et al., 2014; Zhang et al., 2014), which suggests irisin has potential as a promising target for treatment in obesity and type 2 diabetes. In addition to its metabolic effects, irisin has also demonstrated neuroprotective properties, enhancing cognitive function by promoting synaptic plasticity and reducing neuroinflammation. Thanks to these mechanisms, irisin is believed to support brain health and slow the progression of neurodegenerative processes in conditions such as Alzheimer's disease (Lourenco et al., 2020; Park & Poo, 2013).

Additionally, irisin's anti-inflammatory and antioxidant effects support metabolic and cardiovascular disorders and neurodegenerative diseases (Paoletti & Coccurello, 2024). Besides the functions mentioned above, irisin is important in maintaining bone and muscle health by reducing sarcopenia, especially during aging (Guo et al., 2023). It supports muscle growth and regeneration by activating satellite cells and preserving muscle mass (Colaianni et al., 2017; Reza et al., 2017).

2. METHODS

This review is based on a PubMed search using Medical Subject Headings and keywords. Relevant articles published between 2012 and 2024 were included in this review, with the addition of one article published outside the range. All selected studies were evaluated and approved by the co-authors.

3. RESULTS AND DISCUSSION

Table 1 summarizes the key points of irisin's roles in metabolic, neurodegenerative, and cardiovascular diseases, as well as muscle and bone health, discussed in this review.

Table 1. Various functions of irisin

	Role of irisin	**References**
Type 2 Diabetes Mellitus and obesity	improve glucose homeostasis	Boström et al., 2012
	protection against apoptosis caused by hyperglycemia	Song et al., 2014
Neurodegenerative diseases	lower amyloid-β levels	Kim et al., 2023
	improve dopaminergic function	Zhang et al., 2023
Cardiovascular disease	support the heart muscle recovery after myocardial infarction	Zhao et al., 2019
	decrease cardiomyoblasts damage caused by hypoxia	Wang et al., 2017
Muscle and bone health	enhance muscle growth and regeneration after injury	Huh et al., 2014
	promote the healing process after a bone fracture	Kan et al., 2022

Irisin in type 2 diabetes and obesity

Type 2 diabetes (T2DM) is a common metabolic disease caused by insulin resistance and dysfunction of pancreatic β-cells. T2DM affects millions of people globally and contributes to morbidity and mortality. Research has shown that patients with T2DM have decreased plasma irisin levels, suggesting a connection between irisin deficiency and metabolic dysregulation (Liu et al., 2013). This finding has inspired scientists to investigate irisin's role in glucose homeostasis and its potential use in treating metabolic disorders.

The primary function of the pancreas in response to elevated blood glucose levels is to support β-cell function, but only in the early stages of type 2 diabetes mellitus (T2DM). However, prolonged high glucose levels lead to β-cell apoptosis, which results in lower insulin secretion and worse glucose regulation (Liu et al., 2017). The reduction in pancreatic β-cells significantly contributes to the gradual progression of type 2 diabetes mellitus (T2DM). Irisin has been shown to promote the proliferation of human umbilical vein endothelial cells (HUVECs). In addition, irisin protected these cells from apoptosis caused by high glucose levels, demonstrating the protective effect against cellular damage caused by hyperglycemia (Song et al., 2014).

Another study conducted in a mouse model showed that high irisin levels significantly protect kidney function by enhancing podocyte autophagy and reducing glomerular injury and albuminuria. Furthermore, by supporting autophagy leading to preserved

kidney function, irisin may be a promising treatment for diabetic nephropathy (Lai et al., 2023). These findings suggest that irisin may play a crucial role as a protective factor in reducing some of the harmful adverse effects associated with T2DM.

Obesity, a significant risk factor for type 2 diabetes mellitus (T2DM), is closely associated with insulin resistance and reduced irisin production. Studies have shown that obese patients with and without metabolic syndrome have lower circulating irisin levels compared to those with normal weight (Yosaee et al., 2020).

Irisin in neurodegenerative diseases

Alzheimer's disease, one of the most common forms of dementia, is characterized by a progressive neurodegenerative process that leads to memory loss and cognitive decline. The Patho mechanism of AD is associated with the accumulation of amyloid-β (Aβ) plaques, which form from the Aβ precursor protein (APP) and contribute to the development of AD.

Exercise has been commonly recognized for its protective effects against AD, suggesting that physical activity can reduce Aβ levels and decrease amyloid plaque accumulation in the mice brains (Adlard et al., 2005). Recent research has revealed lower irisin levels in the cerebrospinal fluid (CSF) and hippocampus in AD mouse models. These results presented a possibility that irisin deficiency and AD progression are strongly related (Lourenco et al., 2019).

Regarding other promising properties in AD etiology, irisin has shown the capability to lower amyloid-β levels. This effect resulted from increased neprilysin (NEP) levels, a crucial enzyme responsible for Aβ degradation and plaque buildup (Kim et al., 2023). Irisin helps to prevent the accumulation of toxic Aβ plaques, potentially slowing disease progression by enhancing NEP activity.

Furthermore, irisin has shown wider neuroprotective effects. Thanks to its antioxidant and anti-inflammatory properties, irisin helps reduce oxidative stress and inflammation. It also activates brain-derived neurotrophic factor (BDNF), improving cognitive function and preserving synaptic integrity. Additionally, irisin modulates dopamine pathways, which may potentially help reduce common psychiatric symptoms, including apathy and depression (Paoletti & Coccurello, 2024). Higher irisin levels correlate with better cognitive function, as assessed in the Mini-Mental State Exam (MMSE) among AD patients (Lourenco et al., 2020).

It is commonly known that patients with Parkinson's Disease (PD) have mitochondrial dysfunction (Moon & Paek, 2015). In mouse models, the administration of exogenous irisin resulted in decreased dopaminergic dysfunction, apoptosis, and mitochondrial impairment. Furthermore, recent research checked the impact of exercise on irisin levels and balance in PD patients. After 12 weeks of regular exercise, patients exhibited increased irisin levels and improved Berg Balance Scale scores, indicating enhanced balance function and a reduced risk of falls (Zhang et al., 2023). Due to the promising neuroprotective effects discussed above, researchers consider irisin a potential target for developing future therapies for neurodegenerative diseases.

Irisin in cardiovascular disease

Cardiovascular diseases are significant contributors to mortality and a significant burden on public health. Irisin is produced in greater amounts in cardiomyocytes than in skeletal muscle cells (Ho & Wang, 2021). A meta-analysis conducted by Guo et al. showed that patients with coronary artery disease and atherosclerosis had lower irisin levels than those with properly functioning blood vessels (Guo et al., 2020). Additionally, recent research suggests that irisin may protect the heart against ischemic injury. After myocardial infarction, irisin promotes progenitor cells and supports the recovery of heart muscle cells (Zhao et al., 2019).

Wang et al., (2017) demonstrated that irisin enhances heart recovery, particularly by improving coronary flow and functional recovery of the ventricles, reducing infarct size, promoting protective proteins, and inhibiting apoptotic markers such as active caspase 3. In cardiomyoblasts, irisin decreased cell damage and lactate dehydrogenase (LDH) levels caused by hypoxia. Irisin also preserves mitochondrial stability by preventing swelling and optimizing mitochondrial function. These findings suggest that irisin may be used as a potential therapeutic agent for heart protection by enhancing mitochondrial function.

Research indicates that exercise, particularly resistance training, increases irisin and upregulates FNDC5 expression, thereby promoting mitophagy, reducing oxidative stress in the heart muscle, and enhancing heart function. Resistance exercise may become a promising approach for rehabilitation and recovery after myocardial infarction, preventing heart failure (Li et al., 2021).

Furthermore, irisin activates vagus neurons in the nucleus ambiguus, increases calcium levels, induces neuronal depolarization, and leads to bradycardia in rat models (Brailoiu et al., 2015). Additional beneficial properties include the vasodilatation effect via the AMPK-NO pathway, contributing to the prevention of hypertension and its consequences, such as heart muscle remodeling (Fu et al., 2016). Interestingly, patients receiving antihypertensive treatment with amlodipine or valsartan showed higher irisin concentrations

compared to their levels before starting the medication. (Çelik et al., 2015). Due to its multifunctional effects, irisin can be considered for preventing and treating heart diseases.

Irisin in muscle and bone metabolism

Irisin plays a crucial role in maintaining muscle and bone health. Recent research presents irisin as a promising factor for muscle growth and regeneration related to sarcopenia (Guo et al., 2023). Irisin enhances muscle growth in mice and promotes regeneration after injury. Activating satellite cells, increasing protein synthesis, and reducing muscle loss after denervation are significant effects of irisin on muscles, demonstrating potential as a pro-myogenic factor. Huh et al. reported that irisin promotes the expression of genes associated with human muscle growth, particularly those involved in muscle hypertrophy (Huh et al., 2014). Moreover, irisin showed protective effects against muscle loss by maintaining muscle mass under conditions that usually induce atrophy (Colaianni et al., 2017).
In addition to irisin's role in muscle health, the latest studies have shown irisin's beneficial properties in bone health, including promoting osteoblast activity, cortical bone formation, and preventing bone loss (Tsourdi et al., 2022). These effects are especially significant in circumstances that lead to reduced bone density, including mechanical unloading and osteoporosis (Colaianni et al., 2017; Hu et al., 2024). However, another study reveals that irisin stimulates osteoclast progenitors, promoting their differentiation and enhancing bone resorption. These findings emphasize irisin's dual role as a regulatory myokine in promoting bone remodeling (Estell et al., 2020). In bone fractures, irisin administration promotes the healing process by enhancing mineralization and callus formation through the upregulation of osteogenic gene expression. Moreover, irisin stimulated angiogenesis by enhancing the expression of angiogenic genes, which promoted vascular growth at the fracture site (Kan et al., 2022).

4. CONCLUSIONS

Irisin is a multifunctional myokine with a wide range of effects on human health. Due to its various functions, current research highlights irisin as a potential therapeutic target for many chronic conditions. However, further clinical studies are needed to better understand its mechanisms, determine optimal dosing strategies, and assess long-term safety and effectiveness in patients.

Author's Contribution

Methodology - Dominika Kuc, Jakub Klamecki, Aleksandra Garczyk;
Original draft - Dominika Kuc, Jakub Klamecki, Aleksandra Garczyk, Dagmara Skowrońska, Katarzyna Cierpiszewska;
Writing and editing - Dominika Kuc, Dagmara Skowrońska, Katarzyna Cierpiszewska, Jakub Klamecki, Aleksandra Garczyk

Informed consent

Not applicable.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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