Review Paper:

Irisin on Health and Disease across Different Organ Systems-A Comprehensive Review

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Abstract

Irisin, a myokine discovered in 2012, has emerged as a multifaceted hormone with far-reaching implications for human health and disease. Irisin's influence extends to metabolic regulation where it plays a crucial role in energy expenditure, glucose homeostasis and the browning of white adipose tissue. Named after the Greek messenger goddess Iris, Irisin serves as a molecular communicator, transmitting signals of physical activity and metabolic well-being throughout the body. Initially thought to primarily affect skeletal muscle physiology, intriguingly, Irisin is not solely the product of skeletal muscles but is secreted by various other tissues including adipose tissue, the brain and the liver.

The central nervous system's regulation of irisin production has implications for neurodegenerative diseases, cognitive function and mood disorders. Additionally, we discuss the clinical applications and therapeutic potential associated with modulating irisin levels. Understanding the multifaceted role of irisin in health and disease has opened new avenues for interventions and therapies to enhance human well-being. This review provides a comprehensive overview of irisin's diverse roles, shedding light on its profound impact on health and disease.

Keywords: Irisin, Myokine, Homeostasis, Adipose tissue, oxidative stress.

Introduction

Irisin's involvement in metabolic regulation, particularly in the context of energy expenditure and glucose homeostasis, has captivated researchers and clinicians alike[4]. The hormone's ability to stimulate the browning of white adipose tissue and to enhance thermogenesis, has implications for obesity and related metabolic disorder[20]. Furthermore, irisin has been shown to interact with various signaling pathways that modulate insulin sensitivity, making it a potential therapeutic target for diabetes[25]. Beyond its metabolic effects, irisin has also been linked to cardiovascular health[17]. Research has suggested that irisin may have protective effects on the vascular system, influencing endothelial function, blood pressure regulation and the development of atherosclerosis[26].

Inflammatory processes and oxidative stress are also influenced by irisin which can have significant implications for cardiovascular diseases[19]. The skeletal muscle, once thought to be the primary source of irisin, is not the sole contributor to its production[13]. Studies have revealed its secretion by various other tissues including adipose tissue, the brain and the liver[2]. The central nervous system, in particular, has been found to play a pivotal role in irisin's regulation, with potential implications for neurodegenerative diseases, cognitive function and mood disorders[1].

In this review, we will explore the intricate network of signaling pathways through which irisin exerts its effects on different organ systems. Additionally, we will discuss the potential clinical applications and therapeutic avenues associated with modulating irisin levels[18]. Understanding the role of irisin in health and disease across organ systems holds promise for novel interventions and therapies to improve human well-being. As the scientific community continues to unravel the complexity of irisin's functions, this review aims to consolidate current knowledge, highlight knowledge gaps and spark further research in the quest to unlock the full potential of this remarkable hormone[11].

Role of Irisin in Different Organ Systems on Health and Disease

Skeletal Muscle - Guardian of Physical Fitness: Muscle can be categorized into three distinct types: myocardium, skeletal muscle and smooth muscle. It is worth noting that over half of the body's total weight consists of muscle tissue, making it the largest organ in the body[4]. Interestingly, muscle has gained recognition as a secretory organ that can release various substances known as myokines. These myokines play a crucial role in regulating metabolic processes, angiogenesis (the formation of new blood vessels) and growth[1]. They do so through various signaling mechanisms including autocrine (acting on the same cell), paracrine (acting on nearby cells) and endocrine (acting on distant cells) signaling.

Some myokines are produced in response to exercise and these exercise-induced myokines can have positive effects

on the body, particularly in reducing inflammation, both in acute and chronic low-grade inflammatory conditions[19]. When someone begins exercising, gene expression in their muscles changes rapidly and the levels of myokines in their bloodstream also exhibit distinct patterns of change. Mechanisms underlying how exercise impacts myokine function, are not fully understood, but it has been observed that exercise facilitates communication between muscle and adipose (fat) tissue through myokines, promotes interactions between myokines and other cytokines (cell-signaling molecules) and helps to regulate the body's overall inflammatory response.

Physical activity is often linked to improvements in health but the precise mechanisms behind these benefits are still not completely understood, as suggested by Ma and Chen[16] and Motahari et al[19]. One key player in the body's response to physical demands, such as exercise, is the transcriptional regulator peroxisome proliferator-activated receptor gamma coactivators 1 (PGC-1), as highlighted by Arany[1]. Böstrom and colleagues[4] proposed that PGC-1α expression might extend its health benefits beyond muscles by prompting the release of signaling molecules from skeletal muscle. Their research unveiled the role of skeletal PGC-1α in promoting the transformation of subcutaneous adipose tissue into brown adipose tissue (BAT), marked by an increase in BAT-specific genes like UCP1[4]. Based on this discovery, they identified fibronectin type III domain-containing 5 (Fndc5), a gene regulated by PGC-1α, as a likely source of a peptide secreted from skeletal muscle that affects adipose tissue[4].

Fndc5 is known to be a transmembrane protein and it was proposed that it undergoes proteolytic cleavage, allowing the release of a peptide fragment. Although subsequent research has confirmed this proteolytic cleavage, the enzyme responsible for this process remains unidentified[1-3]. Fndc5 is primarily located in the endoplasmic reticulum of a cell and it has been shown that N-linked glycosylation is necessary for Fndc5's stability and the successful release of its cleavage product from skeletal muscle[11,22].

Adipose Tissue - Metabolic Impacts and Weight Management: Adipose tissue exerts significant metabolic influence with irisin playing a pivotal role in orchestrating metabolic processes[4]. Irisin promotes fat browning by converting white adipocytes to metabolically active beige adipocytes, enhancing thermogenesis and energy expenditure within white adipose tissue[4,28]. Beyond energy balance, irisin contributes to weight management and metabolic health, improving glucose homeostasis and insulin sensitivity[2,3,29]. The association of irisin with higher energy expenditure suggests potential benefits for general health and physical fitness[2,3]. Regarding disease implications, irisin emerges as a promising therapeutic target for obesity[4,9] while its role in improving insulin sensitivity positions it as relevant in addressing metabolic syndrome[4,23]. Thus, the multifaceted actions of irisin underscore its potential in modulating adipose tissue function and addressing a spectrum of metabolic and disease-related conditions.

Irisin and the Cardiovascular System

Irisin, a peptide of 112 amino acids, is a myokine dependent on PGC-1 alpha and is cleaved from the membrane-spanning protein FNDC5[4]. The heart, being a muscle, expresses a high level of FNDC5 and exercise induces more irisin production in cardiac muscle compared to skeletal muscle[2,3].

In vitro studies have shown that factors like fatty acids and high glucose can inhibit FNDC5 mRNA and protein expression, resulting in lower irisin levels[1,16]. Serum irisin levels were found to be lower in patients with diabetes mellitus and atherosclerosis compared to patients with diabetes alone[12]. Additionally, serum irisin levels were lower in patients with stable angina and chronic cardiovascular disease[10,24].

Studies on myocardial infarction (MI) induced rat models revealed a negative relationship between irisin levels and markers of MI such as troponin and CK-myocardial band isoenzyme[5]. This suggests that irisin is not released as a result of cardiomyocyte injury but rather reflects the sufficiency of blood supply[5].

Furthermore, serum irisin levels gradually decrease within 48 hours after acute MI, indicating its potential as a marker to predict the severity of cardiovascular disease[2,3,12]. Lifestyle interventions including regular exercise and dietary supplementation, are beneficial in combating cardiovascular disease[15]. Certain drugs have been shown to upregulate FNDC5 expression and to elevate irisin secretion in humans, although further studies are needed to understand the mechanism fully.

Endocrine System - balancing Glucose and Insulin

The endocrine system, crucial in maintaining glucose and insulin balance, showcases irisin as a significant player within this intricate regulatory network. Studies by Zhang et al[29] highlight irisin's substantial contribution to glucose homeostasis by enhancing insulin sensitivity and regulating blood glucose levels, suggesting promising avenues for treating insulin resistance and associated metabolic diseases, as also noted by Khorasani et al[12]. This positions irisin as a promising target for diabetes management, with implications extending to broader metabolic disorders. The research underscores irisin's potential therapeutic significance in addressing diabetes-related complications. Moreover, its role in balancing glucose and insulin levels suggests a broader impact on metabolic health, as detailed by Zhang et al[29].

Additionally, irisin's involvement in glucose homeostasis may offer insights into its potential effects on cardiovascular health, given the intricate relationship between the endocrine system and cardiovascular function, as proposed by Fu et al[7]. This understanding holds particular relevance for diabetes,

where the interplay between diabetes and cardiovascular complications necessitates exploration of irisin's potential applications in preventing such issues. Thus, irisin emerges as a multifaceted regulator with implications ranging from diabetes management to broader metabolic and cardiovascular health concerns.

Central Nervous System: Influence on Cognitive and Emotional Well-being

The central nervous system plays a crucial role in both cognitive and emotional well-being, with synaptic plasticity being a key determinant of cognitive function. Research suggests that isoniamycin's neurotrophic effects can enhance cognitive abilities by promoting synaptic plasticity, memory formation and learning through mechanisms such as neurogenesis and increased expression of brain-derived neurotrophic factor (BDNF)[27]. Additionally, irisin, another neurotrophic factor, has been linked to emotional well-being by regulating stress response and mood, thereby potentially improving mental health[18]. These neuroprotective qualities of isoflavone and irisin offer promising insights into therapeutic approaches for neurological illnesses like Alzheimer's disease and mood disorders such as anxiety and depression, suggesting a potential avenue for treatment and intervention[18,27].

Furthermore, irisin's role in fostering neuroplasticity could have significant implications for learning processes, cognitive function and overall cognitive wellness[27]. Overall, understanding the interplay between neurotrophic factors, synaptic plasticity and emotional regulation provides a foundation for exploring novel treatment strategies for neurodegenerative diseases and mood disorders, potentially improving the quality of life for individuals affected by these conditions[18,27].

Liver: Metabolic Homeostasis and Beyond

Irisin emerges as a pivotal regulator of metabolic homeostasis, particularly in the liver where it exerts influence over fat and glucose metabolism, thereby promoting overall metabolic well-being. Its role extends beyond metabolic regulation to impact liver function, offering potential therapeutic avenues for metabolic liver disorders through modulation of lipid metabolism and hepatic insulin sensitivity. Understanding the implications of irisin's effects on the liver holds significant promise for addressing conditions such as non-alcoholic fatty liver disease (NAFLD) and other metabolic liver diseases, potentially opening doors to innovative treatment strategies. In terms of health implications, irisin's ability to preserve metabolic equilibrium in the liver underscores its potential in promoting metabolic health and averting metabolic illnesses.

Furthermore, its influence on hepatic insulin sensitivity and lipid metabolism suggests a role in enhancing liver function which could help to mitigate liver-related problems. Looking at disease implications, irisin's impact on liver metabolism positions it as a target for NAFLD therapies, offering new avenues for intervention in this prevalent liver disorder. Additionally, understanding irisin's function in various metabolic liver diseases may pave the way for the development of novel treatment modalities, benefiting individuals afflicted with these conditions[7].

Immune System: Inflammation and Oxidative Stress Modulation

Irisin plays a crucial role in immune system modulation, impacting both inflammation and oxidative stress regulation. Studies suggest that irisin acts as a regulator of inflammation, controlling cytokines involved in inflammatory processes and promoting immunological homeostasis by reducing inflammatory reactions[6]. Additionally, irisin exhibits antioxidant properties which contribute to its ability to modulate immune cell oxidative stress, thus safeguarding cells from oxidative damage and enhancing cellular health[14]. Understanding irisin's effects on the immune system offers insights into its broader influence on immunological function, highlighting its potential to regulate immune responses through the control of oxidative stress and inflammation[6].

In terms of health implications, irisin's ability to promote immunological homeostasis by reducing inflammation and oxidative stress suggests its role in maintaining a well-balanced and controlled immune response, while its antioxidant qualities indicate potential benefits in protecting immune cells and fostering cellular resilience[6,14]. Looking at disease implications, irisin emerges as a potential therapeutic target for inflammatory illnesses due to its ability to modulate inflammation, offering opportunities for interventions in conditions where immune system dysregulation plays a significant role[6]. Furthermore, its antioxidant properties suggest potential applications in conditions associated with oxidative stress, indicating its potential to prevent or to treat illnesses characterized by increased oxidative stress on the immune system[14].

Future Therapeutic Prospects: Targeting Irisin for Health Improvement

Targeting irisin for therapeutic purposes holds promising prospects for improving various aspects of health. Its role in maintaining metabolic homeostasis suggests potential applications in treating metabolic diseases such as obesity and insulin resistance[7]. Additionally, irisin's neuroprotective properties offer hope for therapeutic interventions in neurological illnesses, particularly in mitigating cognitive decline associated with conditions like Alzheimer's disease[27]. Moreover, irisin's impact on immune modulation presents opportunities for addressing immune-related illnesses characterized by dysregulated inflammation[6].

However, several challenges and considerations must be addressed. Determining optimal dosage and administration methods remains a challenge, requiring further research to enhance bioavailability and delivery efficiency[14].

Moreover, bridging the gap between preclinical findings and clinical applications necessitates extensive translational research efforts[7]. Despite these challenges, the overall outlook for irisin-based therapies is promising. Adopting a holistic approach to health improvement leveraging irisin's multifaceted effects on various organ systems could lead to comprehensive therapeutic strategies[7]. Such endeavors would require multidisciplinary cooperation, integrating expertise from immunology, neuroscience and metabolism to develop effective treatment plans[6]. In essence, harnessing the therapeutic potential of irisin offers a pathway towards enhancing overall health and well-being through collaborative and interdisciplinary efforts[6,7,14,15].

Conclusion

This thorough analysis concludes by highlighting the diverse function of irisin in bridging health and illness across several organ systems. Originally discovered to be a myokine, irisin is now recognized as a critical hormone influencing many aspects of immunological modulation, metabolic control, cardiovascular health and neuroprotection. Irisin provides potential treatments for obesity, metabolic syndrome and associated conditions by promoting the browning of white adipose tissue, boosting thermogenesis and enhancing glucose homeostasis. Furthermore, its impact on the development of atherosclerosis and endothelial function in the cardiovascular system highlights its potential as a biomarker and therapeutic target for cardiovascular illnesses.

Furthermore, irisin may have therapeutic promise for neurological and mood disorders like depression and Alzheimer's disease due to its effects on the central nervous system, particularly its roles in synaptic plasticity, memory formation and mood regulation. Furthermore, irisin's broader implications for inflammatory disorders and metabolic liver diseases are highlighted by modulation of liver metabolism and impacts on immune system function.

All things considered, irisin targeting for medicinal purposes shows potential for enhancing a number of health issues including immune-related illnesses, metabolic disorders, cardiovascular ailments and neurological disorders. To realize the full clinical potential of irisin-based medicines, however, issues like translational research, appropriate dosage optimization and interdisciplinary collaboration must be resolved. Through the utilization of irisin's diverse effects on various organ systems, it is possible to create all-encompassing therapeutic approaches that improve human health and address a range of ailments.

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