Review Article

IRISIN: A NEWLY DISCOVERED NOVEL MYOKINE

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ABSTRACT

The name irisin was given after the Greek messenger goddess Iris. It is secreted by muscles during exercise. Irisin enhances lipolysis and inhibits hepatic cholesterol synthesis. Acute exercise markedly increases irisin levels and is correlated mainly with ATP levels.

A positive correlation exists between plasma irisin and muscle mass, glucose, ghrelin, IGF1, and BMI. Plasma irisin levels are reduced markedly in patients with type 2 diabetes. Irisin levels are negatively associated with age, serum cholesterol, serum insulin, and serum adiponectin levels. Irisin induces the browning of subcutaneous white adipocytes. It increases aerobic capacity. In the liver, irisin promotes the synthesis of glycogen and inhibits gluconeogenesis. It may contribute to the beta cells profile ration. Irisin has an antioxidant effect. It induces endothelial angiogenesis.

Key Words: Exercise, BMI, Muscle

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STRUCTURE OF IRISIN

Bostrom et al 2012 for the first time identified it while searching for secretions by muscle in response to PGC-1α activation having systemic metabolic effects.[1] PGC-1α has been established as a major regulator of many good remodeling effects induced by exercise in muscle.[2]

Irisin is a 112 amino acid containing polypeptide having a molecular weight of 12 kDa. X-ray crystallography has revealed a structure that has an N-terminal domain and a C-terminal tail.[3] FNIII domains are found in the extracellular domains of many receptors.[4] Human and mouse irisinhas100% structural homology.

Fibronectin type II domain that contains protein 5 (FNDC5) in skeletal muscle secretes irisin. Expression of FNDC5 is stimulated in muscle by PGC-1α in response to exercise.

FNDC5 is a glycosylated type I membrane protein with a 29-amino acid signal sequence at its N terminal, followed by the irisin segment, a linking segment, a transmembrane domain, and a 39 amino acid cytoplasmic domain. Cleavage in the linking peptide by an unknown protease releases irisin into the extracellular milieu.[3] (Figure 1).

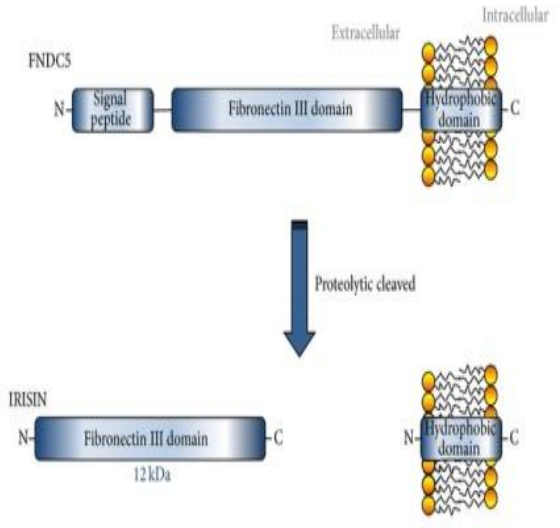

Figure 1. Structure of FNDC5 and irisin secretion.[5]

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MECHANISM OF ACTION

Irisin can bind to proteins of the αV class of integrins.[6] Zhang et al. elucidated, that r-irisin administration increases UCP1 in adipose tissue through the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) and extracellular signal-related kinase (ERK) signaling pathways.[7] Moreover, FNDC5 overexpression promotes Akt phosphorylation, which is known to mediate the effects of insulin on glucose metabolism.[8] Irisin has also been shown to increase lipid breakdown via the cAMP–PKA–HSL/perilipin pathway.[9] Irisin inhibits hepatic cholesterol synthesis through successive activation of AMPK and downregulation of SREBP.[10]

DURATION OF ACTION

Acute exercise significantly raises irisin levels and has been correlated mainly with ATP levels. The raised irisin level during exercise has been shown to fall 30 minutes after the end of the exercise. The strong short-term effect of the irisin is to restore adenosine triphosphate (ATP) and once obtained, it decreases to basal level.[11]

TISSUES DISTRIBUTION OF FNDC5/IRISIN GENE

Tissue-specific studies have shown that the gene for FNDC5 is predominantly expressed in human skeletal muscle. Sufficiently high expression is also present in cardiac muscle and smooth muscle of cerebral arteries and the terminal part of the colon.[12]

Low levels of FNDC5 mRNA have been demonstrated in vital organs like the kidney, liver, lung, and fat.[12] Even though sc-WAT is one of the main targets of irisin action, its expression in adipose tissue is about 1/100th the expression in muscle.

FACTORS AFFECTING IRISIN LEVELS

Plasma irisin levels are positively related to muscle mass, glucose, ghrelin, IGF-1, and BMI. A study revealed that levels of irisin were significantly declined after bariatric surgery, indicating its positive relationship with BMI.[11]

On the other hand, irisin levels are negatively associated with age, cholesterol, insulin, and adiponectin levels.[11] Irisin levels are greater in young male athletes than in middle-aged obese women.

Marked reductions in irisin levels have been reported in patients with type 2 diabetes, especially those having complications.[13,14] Insulin resistance completely changes the metabolism of myocytes, and secretion of myokines during exercise in type 2 diabetics.[15]

PHYSIOLOGICAL ACTIONS OF IRISIN

Irisin induces browning of subcutaneous white adipocytes:

There is a wide difference between white adipose tissue (WAT) and brown adipose tissue (BAT) in their metabolic functions. WAT is a storehouse of triglycerides whereas BAT promotes heat production and energy consumption by expressing UCP1.[6] Previously, BAT was thought to only help in body temperature regulation in infants and did not have much significance in adults. However, WAT contains cells that have the potential to greatly express UCP1 and transform into bright/beige cells that are adaptive brown cells. Moreover, these adaptive brown cells present in WAT are from a different lineage than the BAT. For the browning of fat, exercise is the most important factor, other factors include (1) beta-amino isobutyric acid (2) gamma-aminobutyric acid (3) PPARɣ agonists (4) JAK inhibition (5) Irisin.[16]

Irisin intermediate the advantageous effects of physical activity on metabolism by triggering ‘Brite fat’ development in subcutaneous adipocytes.[1] (Figure 2). The browning of sc-WAT is mediated by irisin-induced phosphorylation of the p38 mitogen-activated protein kinase and extracellular signal-related kinase (ERK) signaling pathways.[7] Irisin increases energy expenditure, promotes weight loss, and

decreases insulin resistance due to fat accumulation.

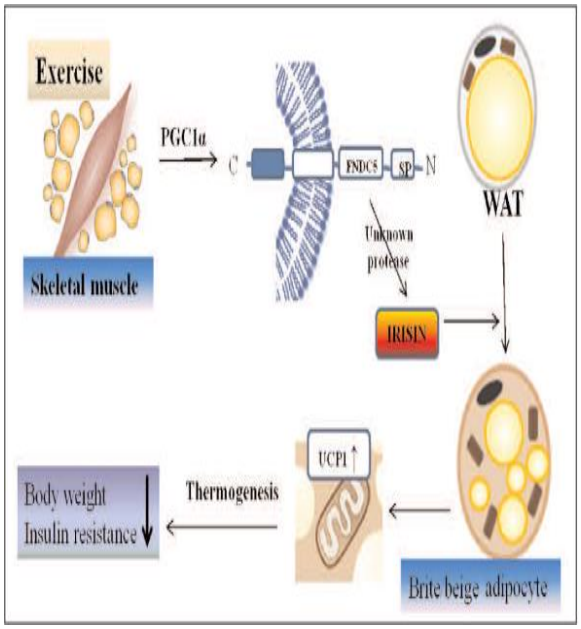


Figure 2: Irisin-induced browning of white adipocytes.[16]

Irisin increases aerobic capacity:
The FNDC5 and PGC-1*α* genes expression has been correlated with exercise through maximal oxygen uptake (VO_2max) and gas exchange (VE/Vco2). Between PGC-1*α* and FNDC5 genes and exercise a significant positive correlation was obtained.[17]

Irisin promotes hepatic glycogen synthesis and inhibits gluconeogenesis:
In an STZ-high fat diabetic mouse model, continuous subcutaneous infusion of irisin improved insulin response, reduced FBG levels, increased glycogen synthase kinase 3 and Akt phosphorylation, glycogen content, and irisin level. It also inhibited phosphorylation of glycogen synthase and glucose-6-phosphatase expression in the liver.[7] It was shown that the effects of irisin to reduce gluconeogenesis were through PI3K-Akt-FOXO1 mediated downregulation of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6 phosphatase and to increase glycogenesis via activation of glycogen synthase,[7] thus indicating that irisin may be effective in decreasing insulin resistance in type 2 diabetes. (Figure 3)

Irisin-betatrophin axis may contribute to β cell proliferation
Irisin administration stimulates the expression of an adipokine, betatrophin, which has been shown to promote pancreatic β-cell proliferation.[18] This finding suggests that increased betatrophin expression by irisin may partly explain its anti-diabetic effect. This association is, however, still controversial and needs further validation.

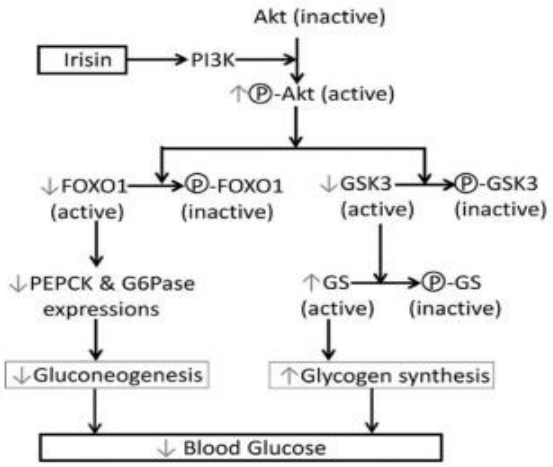


Figure 3: Effect of irisin on hepatic glucose output.[5]

Irisin's effect on lipid metabolism:
The effect of irisin on the metabolism of fat has been reported to be controversial. Most studies reported a negative correlation between irisin and lipid derangement. Increased expression of FNDC5 decreases plasma lipids and glucose in obese mice.[9,10] In a Chinese population, a positive correlation was found between serum irisin and total cholesterol, LDL cholesterol, and free fatty acids. Reduction of irisin due to energy restriction was associated with a decline in total cholesterol and HDL cholesterol.[19-21]

In a study conducted by Tang et al, infusion of irisin for two weeks resulted in a reduction of plasma and hepatic cholesterol in HFD-fed obese mice. It was shown that these effects were induced by successive activation of AMPK and downregulation of SREBP2.[13] (Figure 4). SREBP2 is a transcription factor responsible for the

activation of genes involved in cholesterol synthesis.

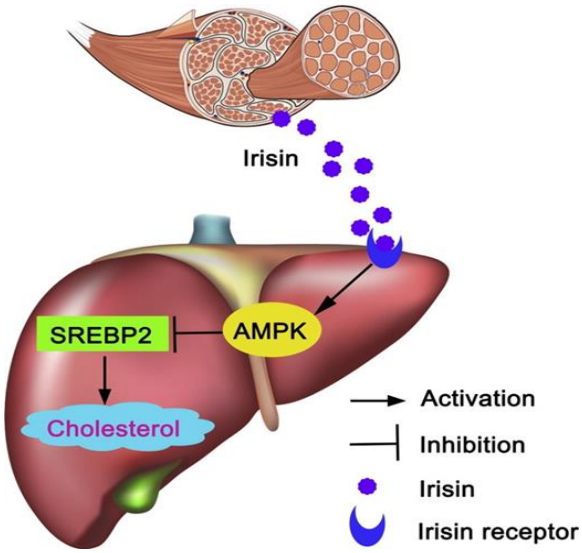


Figure 4. Effect of Irisin on hepatic cholesterol synthesis.[10]

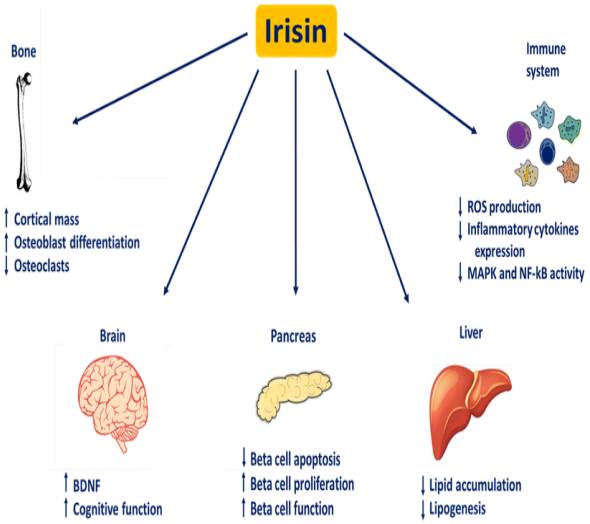
Anti-oxidant effect of irisin:
Irisin, by reducing oxidative stress, has been shown to improve endothelial dysfunction and protect against atherosclerosis**.** Recombinant irisin significantly controlled atherosclerosis in apolipoprotein E-deficient mice.[22] There was a significant reduction in ox-LDL activated biomarkers infiltration of macrophages and T cells within the atherosclerotic plaque by reducing the expression of inflammatory biomarkers. The effect of irisin on human umbilical vein endothelial cells has also revealed that irisin improves endothelial function by suppressing hyperglycemia-induced apoptosis and oxidative stress; along with increasing the expression of antioxidant enzymes.[23]

Irisin induces endothelial angiogenesis:
Recent findings by Fei Wu and colleagues have shown that irisin promotes angiogenesis in a human umbilical vein through stimulation of the extracellular signal regulator kinase (ERK) pathway, proposing that irisin may have a pivotal role in preserving endothelial homeostasis.[24]

Irisin as a biomarker of CVD in diabetes:
In patients with T2DM with macrovascular complications, irisin levels were lower as compared to patients without macrovascular complications, implying that this myokine may be a biomarker of CVD disease in people with T2DM.[14]

Irisin's possible role in the action of metformin:
In a study by Li and colleagues, metformin, promoted the release of irisin from skeletal muscle[25], suggesting that its release could be one of its mechanisms of action.

Other effects of irisin:
On bone: Increased cortical bone mineral density, thickness, and bending strength results when low dose recombinant irisin is given. (Figure 7).[26] This action has been attributed to activation of osteoblasts and a parallel reduction in osteoclast number and activity.
On brain**:** Recombinant irisin administration has been shown to promote hippocampal neurogenesis in mice, proposing its possible role in improving memory.[27] FNDC5 expression was shown to increase in the hippocampi of mice taking part in a thirty-day voluntary wheel running regime. FNDC5 expression in the brain upregulates the production of the neurotrophin B DNF,[28] which may have a role in mediating its beneficial effects in neural tissue (Figure 5).
Anti-aging effect: Plasma irisin levels showed a significant association with telomere length.[29] It is known that irisin signaling activates p38 MAPK which controls the expression of human telomerase reverse transcriptase.[30]
Anti-cancer effect: According to a recent study, irisin has an inhibitory effect on the amount and metastatic properties of neoplastic breast cells[31] and has also been shown to suppress proliferation in lung carcinoma.[31]



BDNF: brain-derived neurotrophic factor; ROS: reactive oxygen species; MAPK: mitogen-activated protein kinase; NF-kB: nuclear factor-kappa B.

Figure 5. Physiological actions of Irisin on bone, brain, pancreas, liver, and immune system.

AUTHOR'S CONTRIBUTION

SA: Manuscript writing
HJQ: Supervision and critical review

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