THE MULTITUDE OF IRISIN'S ESSENCE IN THE BODY

Abstract

Irisin is a new peptide, discovered by Bostrom and his colleagues in 2012. It is a fragment of a membrane protein known as fibronectin type III domain-containing protein 5 (FNDC5). The name 'irisin' is given to emphasize its role as a messenger, produced mainly from muscle (skeletal) and adipose tissue and acts on various parts of the body. This peptide is of major interest because of its therapeutic potential in various diseases. Some important aspects of the action and uses of irisin are discussed here, including its relation with the various physiological and pathological conditions of the body. Although upcoming and current research on irisin seems promising, further elaborate exploration is necessary to elucidate its full potential as a reliable therapeutic agent in prevention and treatment of many diseases.

Keywords: irisin; myokine; adipokine; exercise; diabetes

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I. INTRODUCTION

Irisin is an adipomyokine, discovered by Bostrom and his colleagues in 2012. It is a fragment of a protein present in cell membrane known as fibronectin type III domain - containing protein 5 (FNDC5) and comprises of 209 amino acid residues. FNDC5 has a C-terminal fragment which is situated in the cytoplasm, while the N-terminal portion which is located extracellularly is proteolytically cleaved to form irisin which is finally released into the circulation.

Irisin reduces obesity and improves insulin resistance by transforming white to brown adipose tissues. It is released in response to exercise, this provides a hormonal link between exercise and better insulin sensitivity. Irisin is mainly secreted by skeletal muscles, subcutaneous and adipose tissues. Some studies have shown that traces of irisin are also secreted by liver, pancreas, testes, brain, heart, spleen, and stomach. It usually serves to mediate interactions with other molecules (proteins, DNA, etc.) or cells. Hence, the name "Irisin" is derived from "Iris", the Greek messenger goddess like whom it serves as a powerful messenger for specific cells. The peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) induces the process of secreting circulating irisin. It is considered to act on white adipose cells to stimulate the expression of uncoupling protein 1 (UCP1) and modify the expression of various molecules which leads to browning of fat. This development of brown adipocytes and ultimate increase in thermogenesis results in body weight reductions, improved insulin sensitivity and improved glucose tolerance in mice.

It is said that Irisin, by the expression of β-trophin, promotes the proliferation of β-cells of pancreas and improves glucose tolerance. Hence, irisin was postulated to elevate insulin secretion by reducing apoptosis or increasing β-cells proliferation. Further studies are, however, needed to elucidate the molecular mechanisms behind the connection of irisin with β-cell function and its function in insulin secretion in normal glucose tolerance. Several studies have concluded that irisin alleviates insulin resistance and type 2 diabetes mellitus (T2DM) by sensitizing the insulin receptor in skeletal muscle and heart, thereby browning the white adipose tissue, improving hepatic lipid and glucose metabolism and functions of pancreatic β cell. Therefore, irisin poses as a prospective new target to tackle insulin resistance and T2DM.It was referred that irisin could be cloned through recombinant DNA technology, so that it might be isolated as a drug in the treatment of diabetes mellitus.

Among healthy individuals, the levels of irisin were known to be lesser in males than in females after adjustment for lean body mass. The levels showed a day-night pattern which peaked at 9 pm and rised after exercise. The levels of irisin were unaffected by the consumption of a standardised meal and were un associated with diet quality or caloric intake. Studies indicated that girls had higher irisin levels than boys and that the levels were independently associated with fasting blood glucose. Another study found that irisin levels decreased significantly in T2DM patients compared to controls and there were lower levels in patients with diabetic nephropathy (DN) than in those patients with no complications. Moreover, there was statistically significant negative correlation between irisin and blood pressure, serum creatinine, duration of diabetes, albumin/creatinine ratio, body mass index (BMI), and HbA1c (glycated haemoglobin) in all T2DM patients.

II. ASSOCIATION OF IRISIN WITH VARIOUS PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

Physiological Conditions		Pathological Conditions	
Condition	**Relation with irisin**	**Condition**	**Relation with irisin**
Exercise	Increases irisin secretion	Type 1 Diabetes Mellitus (T1DM)	Increases irisin concentration
Gender	Lower concentration in men	T2DM and Gestational Diabetes Mellitus (GDM)	Decreases irisin concentration
Body Mass Index (BMI)	Positive correlation	Metabolic syndrome (MetS)	Increased level
Pregnancy	Higher levels in pregnancy	Cancer	Lower levels of irisin

III. ASSOCIATION OF IRISIN WITH VARIOUS SYSTEMS OF THE BODY

Cardiovascular System			
Condition	**Relation with irisin**	**Condition**	**Relation with irisin**
Vascular Endothelium	Increases Proliferation	Coronary Artery Diseases (CAD)	Predicts adverse coronary events
Angiogenesis	Proangiogenic Effect	Vascular Diseases	Therapy & Prevention
Bone Metabolism			
Bone formation	Osteoblastogenic effects	Osteoporosis & Osteopenia	Therapeutic effect
Brain/Central Nervous System (CNS)			
Neurogenesis	Enhances	Neurodegenerative disorders	Therapeutic potential

1. **Irisin in Exercise:** During muscle contraction, myokines are secreted that can possibly protect against chronic diseases. Studies have reported a correlation between aerobic activities and FNDC5 expression and PGC-1α genes. These results in the secretion of the myokineirisin by muscles and adipocytes in response to exercise, which converts white adipocytes to brown adipocytes. This browning of white adipocytes and the consequent increase in thermogenesis improves insulin sensitivity, glucose tolerance and body weight reductions.

2. **Irisin and Gender:** The differences of irisin levels in the different genders might be owing to the differences in fat distribution (brown and white) in them. This can also be explained by the hormonal differences in the different genders. Estradiol (primary female sex hormone) is known to correlate positively with irisin levels, while no significant relationship was found with free testosterone levels.

3. **Irisin with BMI:** Positive association of irisin with BMI was reported in various studies which could be explained partly by the muscle mass and percentage of fat mass. This could support the concept of the possibility of irisin resistance in case of obesity.

However, there have been reports of both positive and negative correlations with BMI and waist-hip ratio, according to the studied population.

4. **Irisin in Pregnancy:** Irisin levels were found to be elevated in normal pregnant women. Studies have suggested that pregnant states and the placenta may take part in increasing irisin levels. Immunohistological staining has localized irisin to the cytoplasm of cytotrophoblast, syncytiotrophoblast and decidua of the placenta.

5. **Irisin in Type 1 Diabetes Mellitus:** Elevated irisin levels were found in adolescents and children with T1DM compared to controls by certain studies. In patients with continuous subcutaneous insulin infusion, better metabolic control was seen with elevated irisin levels and there was association of irisin and better glycemic control. Insulin requirement and irisin was observed to be negatively correlated. Betatrophin is a hormone secreted by adipose tissue and liver that has the potential to ameliorate metabolic control in mice by causing proliferation of β cell in response to insulin resistance. Positive correlation of irisin with total betatrophin has been reported in T1DM patients.

6. **Irisin in T2DM and GDM:** Circulating irisin levels were significantly lesser in patients with T2DM and GDM compared with non-diabetic controls. Decreased irisin level in T2DM patients can be explained by reduced activity of PGC-1α in the muscle tissue of these patients. This reduced PGC-1α activity results in decreased FNDC5 synthesis and decreased production of irisin. Moreover, the resultant hyperglycemia and increased free fatty acid levels owing to insulin resistance, also leads to a reduced PGC-1α activity.

7. **Irisin in Metabolic Syndrome:** In cases with MetS, irisin concentrations were significantly higher than those without MetS. There was association of irisin with increased risk of MetS, denoting either elevated secretion of irisin by muscle or adipose tissue or a compensatory increase to overcome an underlying irisin resistance. Increased irisin may be due to decline in insulin sensitivity, glycolytic and lipid metabolism, with a positive feedback mechanism of irisin and adiponectin to increase the consumption of energy in the adipocytes.

8. **Irisin in Cancer:** Irisin levels have been reported to be significantly lower in cancer patients especially in breast cancer. Irisin has the ability to reduce the number of malignant (mammary) cells by inducing apoptosis. Moreover, it decreases the viability and spread of these cells. Malignant mammary cells are sensitized by irisin for chemotherapeutic treatments without affecting nonmalignant cells. It could, therefore, be a used as adjuvant therapy for some cancers.

9. **Irisin in Cardiovascular System:** Irisin administration is known to significantly increase endothelial cells proliferation through the ERK pathway (extracellular signal - regulated kinase pathway). Proangiogenic effects of irisin have also been demonstrated particularly in the process of stimulation of capillary structures and cell migration. It also protects endothelial cells in the body by the activation of ERK pathway. Many studies have suggested that one of the molecular mechanisms by which irisin exerts its action is via phosphorylation of the ERK pathway. Irisin is found to predict adverse coronary events in patients with CAD. It has also been proposed for preventive and therapeutic uses for cardiovascular diseases.

10. **Irisin in Bone Metabolism:** Irisin has been demonstrated to promote osteoblast differentiation. It was found that osteoblastogenic changes are attributed to a mechanism dependent on irisin. Administration of low doses of irisin showed anabolic effects in the mineral density of cortical tissue and bone mass, reductions in osteoclasts, increased expression of osteoblastic genes and decreased expression of osteoblastic inhibitory genes. Irisin was demonstrated to exert its osteoblastic effects by means of the signal pathway where there is activation of p38 mitogen-activated protein kinase (p38 MAPK) and ERK. Irisin levels were found to be decreased in women with osteoporotic fractures. This can be attributed to the possible positive impact of irisin on bone quality. Irisin has, therefore, been proposed as a myokine with a possible therapeutic outcome for gaining bone mass in osteopenia and prevention of osteoporosis.

11. **Irisin in Brain/Central Nervous System**: It isreported that irisin and FNDC5 are secreted by Purkinje cells in rodent cerebellum. In humans, irisin was found in cerebrospinal fluid and detected to be expressed in the neurons present in the paraventricular nucleus. Neuropeptide Y, which regulates appetite, is also expressed in the paraventricular nucleus. This suggests that irisin possesses central metabolic functions. Reportedly, irisin is probably involved in the neuroprotection of physical activities for diseases like cerebral ischemia via the activation of Akt and ERK1/2 pathways along with protection from brain damage. Administration of irisin has found to increase neurogenesis via the STAT3 (signal transducer and activator of transcription 3) signalling pathway. Since irisin promotes favorable processes in the CNS, its therapeutic prospects should be explored in neurodegenerative disorders.

IV. FUTURE PROSPECTS

Irisin, a novel peptide secreted by muscle, has been demonstrated to relate to various metabolic conditions. It has been regarded as a possible treatment, where it could be used as injection using recombinant DNA technology, for diabetes and therapy in many disease conditions. However, there have been some controversial results in the many studies conducted on irisin especially regarding studies on humans. Moreover, it is presently unclear about the precise effect of irisin as a potential therapeutic agent for diseases like T2DM, metabolic syndrome etc. Therefore, the future poses a challenge to conduct deeper research for identification of a possible clinical application.

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