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Role of Irisin in Physiological and Pathological Conditions: Review Article

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ABSTRACT

The chance of developing several illnesses, such as obesity, diabetes, heart disease, some types of cancer, and some neurological conditions, is increased by a sedentary lifestyle or a lack of exercise. Exercise lowers the risk of numerous diseases and helps to enhance quality of life. Irisin, a hormone released during exercise that connects muscles to other tissues, is a fragment of the cell membrane protein FNDC5. Over the past ten years, it has become abundantly clear that irisin is a molecular mimic of exercise and has a variety of advantageous effects, such as browning of adipocytes, alteration of metabolic processes, control of bone metabolism, and nervous system function. Irisin plays a part in the development of cancer; various studies have demonstrated how it affects the invasion, migration, and growth of cancer cells. Irisin's receptor is not fully understood, however, it probably works through a specific family of integrin receptors in some tissues. In this article, we examine recent studies, which suggest that irisin may be a useful therapeutic agent for the treatment or prevention of a number of disorders with a metabolic component. This paper describes the irisin's biochemical and structural characteristics and offers information on how irisin functions in various clinical circumstances.

INTRODUCTION

Irisin is a hormone that was identified in 2012 and is mostly produced by muscles and adipose tissue. It regulates many physiological and metabolic pathways. When the PPAR co-activator-1 (PGC-1) is stimulated by an event like physical activity, it cleaves the fibronectin type III domain-containing protein 5 (FNDC5) into a 112 amino acid peptide [(1)].

PGC-1 is a multifunctional transcriptional co-factor that affects fatty acid and glucose metabolism as well as mitochondrial biogenesis and function. It can be activated by a variety of dietary and physiological inputs. The transmembrane FNDC5 protein's expression and production are both stimulated by PGC-1 [(2)].

A glycosylated type I membrane protein called FNDC5 has a transmembrane domain (171-209 amino acids), a fibronectin III domain (33-124 amino acids), and a N terminal signal peptide (1-28 amino acids) [(3)]. Moreover, **Mahajan and Patra** [(4)] reported that the type I membrane protein, whose proteolytic breakdown produced the release of the protein's N-terminal portion into extracellular space, is the source of FNDC5. In addition, **Seifi *et al.*** [(5)] reported that the mouse chromosome 4 and human chromosome 1 both contain the FNDC5 gene.

Schumacher *et al.* [(6)] reported that irisin is released following the proteolytic cleavage, glycosylation, and likely dimerization of FNDC5, which contains the majority of the fibronectin III domain and has a same amino acid sequence in both humans and mice. FNDC5 has a molecular weight of between 12-32 kDa. All mammalian species have well maintained irisin hormone, and mice and humans have 100% identity [(1)].

After being secreted by working skeletal muscle, irisin binds to white adipose tissue (WAT) cells through an unknown receptor [(1)]. **Schumacher *et al.*** [(6)] showed that irisin is a premade dimer that may be crucial for ligand receptor binding. The protein N-terminal is a potential candidate for interaction with an undiscovered receptor because irisin has two loop sections made up of residues 55-58 and 106-108 **(Figure 1)**.

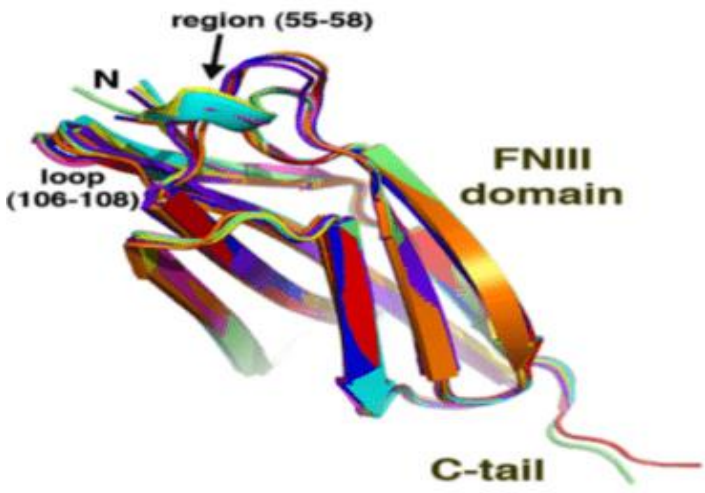

Figure (1): Structure of the irisin dimer [(6)]

There are two types of receptor activated dimerization, including binding of a single ligand that causes dimerization of two receptors or binding of two monomeric ligands that encourage dimer interactions between monomeric receptors. The irisin

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structure suggests a mechanism for myokine ligand signaling through binding of a preformed dimer [6].

Role of irisin in physiological and pathological conditions

One of the most significant of irisin's many known physiological effects is to encourage the WAT's browning and uncoupling protein 1 (UCP1) expression. Irisin enhances systemic metabolism in this way, increasing energy expenditure, which leads to weight loss, improving increasing muscle strength and glucose metabolism, both of which have an impact on obesity [1].

1. Irisin and exercise

It is thought that the hormone irisin, which myocytes secrete, acts as a link between exercise and metabolic balance. The quantity of muscle mass and the concentration of irisin are positively correlated [7].

Huh *et al.* [8] discovered beneficial correlations between body mass index (BMI) and FNDC5 mRNA expression in human skeletal muscle. In addition, **Park *et al.*** [9] uncovered a link between human plasma irisin levels and weight, BMI, waist size, and fat mass.

Lowell and Spiegelman [10] found that PGC-1 was shown to activate mitochondrial genes, which regulated thermogenesis in mouse brown adipose tissue and skeletal muscle. UCP1, a protein found inside the mitochondrial membrane, delivers protons to the mitochondrial matrix from the intermembrane area.

2. Irisin-induced browning of white adipocytes

Adipose tissues are often divided into WAT and brown adipose tissue (BAT). The principal location for storing lipid and energy is WAT, but BAT can release energy as heat as a result of mitochondrial uncoupled respiration. UCP1, a specific mitochondrial protein, facilitates this process [11].

Adipocytes from WAT contain unilocular lipid droplets, few mitochondria, and a relatively moderate metabolic rate in contrast to adipocytes from BAT, which have multilocular lipid droplets, numerous mitochondria, and a very high metabolic rate. The sympathetic nervous system innervates the highly vascularized BAT tissue. In the human fetus during gestation, BAT develops. As a result, the amount of UCP1 rises throughout fetal development, peaks at delivery, and then falls off over the following nine months [12].

Adult humans can detect BAT in the supraclavicular, neck, paravertebral, and suprarenal locations [13].

Numerous studies have noted higher irisin levels in obese subjects. But after gastric band surgery, obese patients' irisin levels dropped significantly, indicating that the procedure has a protective feedback mechanism to counteract metabolic disturbances [14]. Moreover, **Crujeiras *et al.*** [15] reported that irisin may be utilized as a biomarker for poor or changed metabolic status in persons who are obese.

The mitochondrial protein UCP1 plays a major role in the thermogenic capacity of brown fat. Cold exposure and/or -adrenergic signaling can upregulate UCP1 expression. It stimulates the production of UCP1 in adipocytes after muscle secretes irisin, which causes WAT to brown via the p38 MAPK and ERK pathways [16].

Mice that have improved insulin sensitivity, glucose tolerance, body weight, and fat mass have browning of their white adipocytes, which increases thermogenesis. **(Figure 2)** [1].

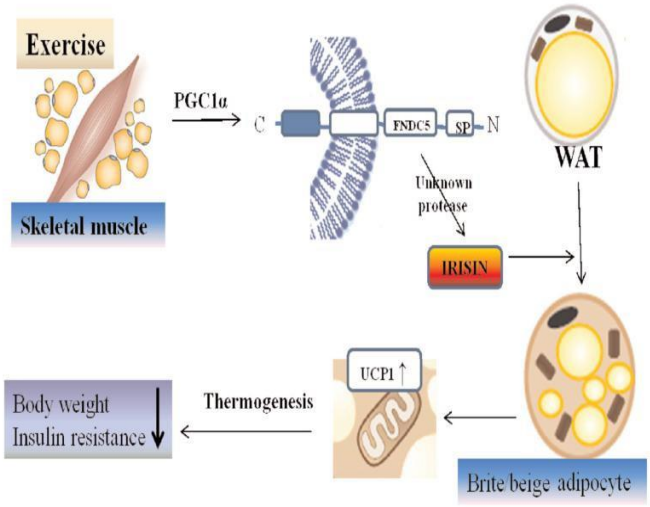

Figure (2): Exercise-induced release of PGC1α from skeletal muscle increases the expression of FNDC5. Cleavage of FNDC5 by an unknown protease releases the irisin. WAT are converted to BAT by irisin. Irisin upregulates the expression UCP1 in outer membrane of mitochondria, which leads to increased thermogenesis by oxidation of fatty acids [1]

3. Improvement of insulin sensitivity

Irisin primarily affects WAT and works to increase calorie intake, which can lessen HFD and prevent the development of insulin resistance (IR) [17]. **Lopez-Legarre *et al.*** [18] has shown that obese

patients with metabolic syndrome who underwent an 8-week low-energy diet treatment saw a noticeable drop in body weight and a rise in basal irisin levels. High irisin levels were strongly linked with lower levels of glucose and insulin as well as lower carbohydrate intake, indicating that irisin might play a part in controlling glucose metabolism in HFD-induced obesity.

4. Irisin and pancreas

Irisin is favorably correlated with circulating insulin levels in those with normal blood sugar levels in humans, suggesting that irisin may be regulating-cell function [19].

Muscle stimulation was found to boost PGC-1 expression, which in turn stimulated FNDC5 expression and cleavage to produce irisin, which sped up the browning of WAT, increased energy consumption, encouraged insulin production, and promoted beta cell regeneration. which enhances glucose tolerance and decreases IR [20].

Irisin inhibits apoptosis in pancreatic beta cells and promotes their proliferation, as well as the production and release of insulin. Thus, irisin levels in the blood can enhance glucose tolerance and lessen insulin resistance **(Figure 3)** [21].

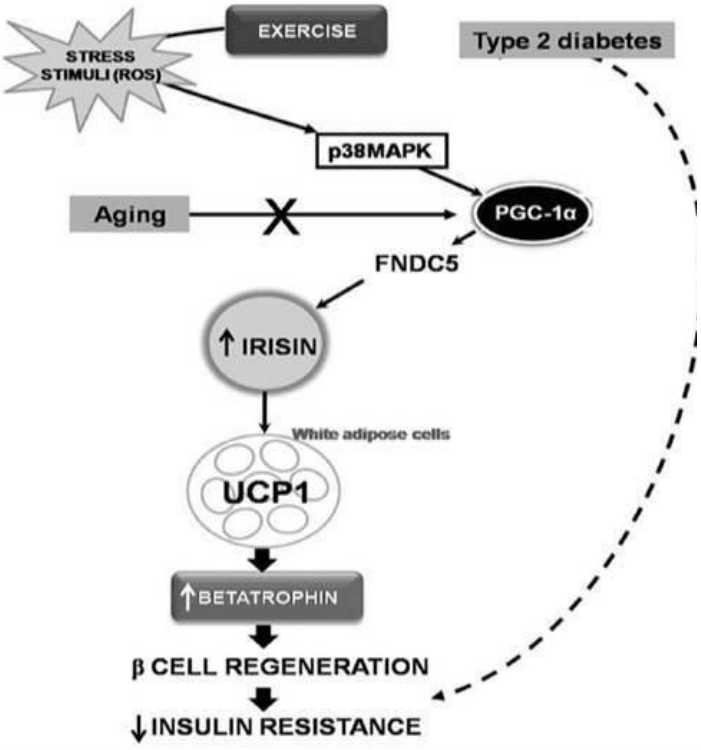

Figure (3): Irisin–betatrophin pathway and its possible implications in insulin resistance[21]

3. Irisin and bone mass:

Due to cortical bone's great sensitivity to anabolic substances generated by muscle, exercise has a positive impact on bone metabolism [22] **(Figure 4).**

Anastasilakis *et al.* [23] described a connection between women in postmenopause with decreased bone mass and low irisin concentration in the blood and osteoporotic fractures.

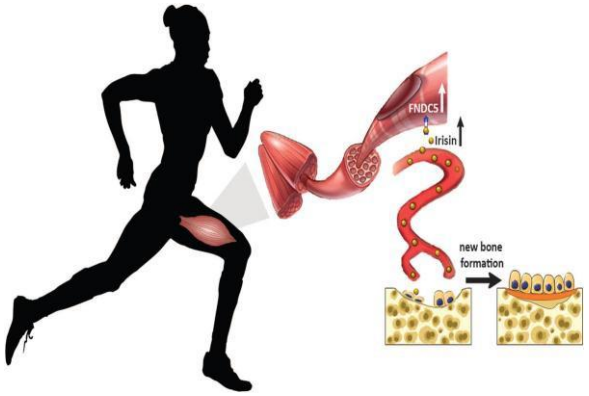

Figure (4): Through direct stimulation of osteoblasts' differentiation and activity, the myokine irisin, which is produced by skeletal muscle during exercise, enhances the strength and quality of bones [24].

4. Enhancement of cognitive capacity

Physical activity has been shown to significantly improve cognitive performance, especially in older people who are more prone to degenerative nerve disorders [25].

Erickson and Kramer [26] revealed that exercise-induced increases in hippocampus volume had a clear link with cognitive ability, confirming that physical activity can modify the anatomical structure and physiological function of the brain.

Midbrain, pons, cerebellum, and olfactory bulb of the mouse brain had FNDC5 mRNA, however the hippocampus did not [27].

5. Irisin and ageing

Further research is needed to determine whether plasma irisin can predict telomere length in healthy individuals and whether it has any potential anti-aging effects. A chromosome's ends are guarded against degradation and fusion with nearby chromosomes by regions of repeating nucleotide sequences known as telomeres [14].

Human telomerase reverse transcriptase (hTRT), telomerase's catalytic subunit, controls telomerase activity. It has been demonstrated that P38 MAPK

controls hTRT expression. It's important to note that irisin has been proven to activate the MAP kinase signaling pathway [16]. Although exercise is linked to longer telomeres, the function of irisin in the aging process is unknown.

6. Irisin and cardiovascular system

Zhang *et al.* [28] reported that irisin was administered to the third ventricle, where it was shown to raise blood pressure and cardiac contractility by activating neurons in the paraventricular nuclei of the hypothalamus. Increases in oxygen consumption, carbon dioxide production, and heat production were observed when irisin was injected centrally, indicating that the CNS may have had a role in the increase in metabolic activity.

However, irisin intravenous injection reduced blood pressure without altering cardiac contractility. Irisin's vasodilator function, which affected both endothelial cells and smooth muscle cells, was thought to be the cause of the drop in blood pressure brought on by peripheral injection [28].

7. Irisin and thyroid function

Thyroid hormones control thermogenesis, the basal metabolic rate, and the metabolism of proteins, carbohydrates, and lipids. One of the most prevalent endocrine illnesses, thyroid dysfunction is linked to metabolic imbalance, poor energy homeostasis, oxidative stress, and muscular problems [29].

Thyroid hormone controls the expression of several genes, including PGC1 through thyroid hormone receptors (TRs). Given that PGC1 is a potent coactivator of TRs, it is most likely a significant modulator of a few thyroid hormone actions. There is evidence that thyroid hormone induces PGC1 expression in a variety of organs [30].

8. Irisin and fatty liver disease

Exercise is a crucial part of the lifestyle adjustment that can help people with non- alcoholic fatty liver disease (NAFLD). Although the mechanism underlying this exercise- induced liver fat reduction was unknown, it was shown that plasma irisin levels negatively correlated with intrahepatic triglyceride levels, indicating that irisin may play a role in the pathogenesis of NAFLD [31].

Low density lipoprotein (LDL) and low high density lipoprotein (HDL) levels are markedly elevated in the atherogenic lipid profile of patients with fatty liver disease. On the other hand, increasing intrahepatic triglyceride deposits, with or without related inflammation, is an important part in the pathophysiology of this disease. Strong correlations exist between intrahepatic triglyceride deposition and BMI, waist size, blood pressure, and insulin level, IR, and transaminase levels [32].

9. Irisin and endothelial dysfunction

Impairment of one or more endothelial functions is referred to as endothelial dysfunction. Numerous endothelial functions, including control reduction of inflammation, improvement of vascular tone and organ perfusion, and transendothelial transfer of blood solutes, and inhibition of coagulation, are jeopardized in insulin resistance and diabetes [33].

Endothelial dysfunction is the main driver of the inflammatory pathways that are connected to vascular issues in T2DM patients. Among other things, endothelial cells control platelet activation, fibrinolysis, thrombus formation, tissue growth and metabolism, angiogenesis, inflammation, vessel integrity, hemostasis, vascular permeability, vascular smooth muscle cell proliferation, and blood fluidity maintenance [34].

The endothelium is also in charge of regulating the tone of the blood arteries by generating vasodilators like nitric oxide (NO) and prostacyclin (PGI2) as well as vasoconstrictors like endothelin-1 (ET-1), angiotensin II, and reactive oxygen species (ROS). In addition, endothelial cells release plasminogen activator inhibitor-1 (PAI-1), which inhibits fibrinolysis, von Willebrand factor (vWV), and antithrombotic chemicals such NO and PGI2 (which stop platelet aggregation) **(Figure 5)** [35].

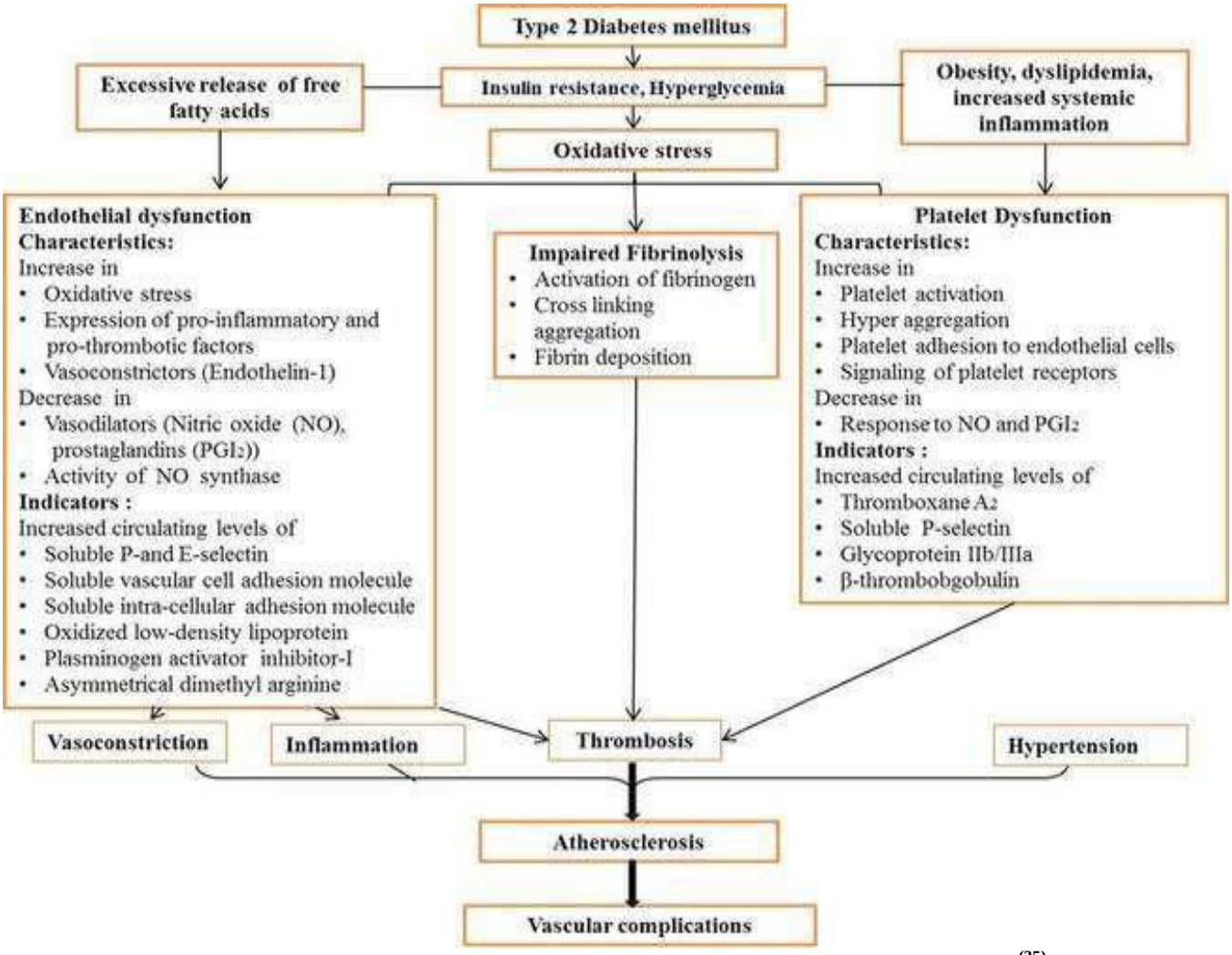

Figure (5): Pathophysiological processes in T2DM patients that result in vascular problems [35].

Irisin has been demonstrated to activate PPAR expression, which could raise adiponectin levels and adiponectin receptors, decrease inflammation associated with obesity in adipose tissue, and increase adiponectin levels, so enhancing endothelial function. Adiponectin increases NO generation and bioactivity and has anti-oxidative and anti-inflammatory properties [35]. Irisin can change white adipocytes into brown adipocytes and may lower circulating FFA levels from adipose tissue to improve endothelial function in obese people by activating the Akt-eNOS pathway. By blocking the Akt signaling pathway, the free fatty acid levels produced from extra white adipose tissue may reduce the ability of eNOS to phosphorylate [36].

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