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Original article

A Review on the Role of Irisin in Insulin Resistance and Type 2 Diabetes Mellitus

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Key Words

Irisin, insulin receptor, insulin resistance, metabolic diseases, metabolic dysfunctions, type 2 diabetes

Abstract

Irisin is a novel hormone like polypeptide that is cleaved and secreted by an unknown protease from fibronectin type III domain-containing protein 5 (FNDC5), a membrane- spanning protein and which is highly expressed in skeletal muscle, heart, adipose tissue, and brain. Since its discovery in 2012 it has been the subject of many researches due to its potential physiological role. It is believed that understanding irisin secretion may be the key to comprehend many diseases and their development. Irisin is a myokine that leads to increased energy expenditure by stimulating the 'browning' of white adipose tissue. In the first description of this hormone, increased levels of circulating irisin, which is cleaved from its precursor fibronectin type III domain-containing protein 5, were associated with improved glucose homeostasis, reducing insulin resistance. Irisin is a powerful messenger, sending the signal to determine the function of specific cells, like skeletal muscle, liver, pancreas, heart, fat and the brain. The action of irisin on different targeted tissues or organs in human being has revealed its physiological functions for promoting health or executing the regulation of variety of metabolic diseases. Numerous studies focus on the association of irisin with metabolic diseases which has gained great interest as a potential new target to combat type 2 diabetes mellitus and insulin resistance. Irisin is found to improve insulin resistance and type 2 diabetes by increasing sensitization of the insulin receptor in skeletal muscle and heart by improving hepatic glucose and lipid metabolism, promoting pancreatic β cell functions, and transforming white adipose tissue to brown adipose tissue. This review is a thoughtful attempt to summarize the current knowledge of irisin and its effective role in mediating metabolic dysfunctions in insulin resistance and type 2 diabetes mellitus.

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1. Introduction

Diabetes and obesity-related diseases are a major drain on healthcare resources; it is reported that around 350 million people suffer from diabetes globally, being Type 2 diabetes mellitus (T2DM) the most prevalent1. Insulin resistance and/or type 2 diabetes are characterized by a range of metabolic disturbances, such as hyperll guinsulinaemia, enhanced hepatic gluconeogenesis, impaired glucose uptake, metabolic inflexibility and mitochondrial dysfunction [1-3]. Insulin is known to act through a tyrosine kinase receptor, which phosphorylates the insulin receptor substrates (IRS-1 and IRS-2), leading to successive PI3K and protein kinase B (PKB)/Akt activation [4, 5]. The main postprandial actions of insulin include the translocation of GLUT4 to the membrane of cardiac tissues, skeletal

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muscle and adipocytes, activation of glucokinase and inhibition of gluconeogenesis in hepatocytes, and inhibition of lipolysis in adipose tissue [6]. Due to the development of insulin resistance, which is mainly occurred because of the desensitization of the insulin receptor and impaired phosphorylation of its substrates, main postprandial actions of insulin are totally or partially compromised in the type 2 diabetes. The skeletal muscle is particularly important in insulin resistance, as it uptakes most of the postprandial glucose [6, 7].

Many current studies revealed that irisin improves insulin resistance and type 2diabetes by increasing sensitization of the insulin receptor in skeletal muscle and heart, improving hepatic glucose and lipid metabolism and pancreatic β cell functions, and transforming white adipose tissue to brown adipose tissue [1-5].

Numerous studies focus on the association of irisin with metabolic diseases has gained great interest as a potential new target to combat type 2 diabetes mellitus (T2DM) and insulin resistance [4-8]. This review was an attempt to delineate the importance of irisin and its role in mediating metabolic dysfunctions in insulin resistance and type 2 diabetes mellitus.

2. Biochemistry of irisin

Irisin, a novel polypeptide hormone, is proteolytic[ally] processed from fibronectin type. III domain containi[ng] protein 5 (FNDC5), which is highly expressed in skeleta[l] muscle and heart [6, 7]. Recent studies sh[ow] FNDC5 was also expressed in other tissues, such as adipose tissue and liver, which indicates additional functions of this hormone [6-9].

2.1.1. Chemistry of Irisin

Irisin is a hormone like polypeptide including 112 amino acids and is derived from the carboxy terminus of a membrane-spanning protein with 196 amino [acids] known as fibronectin type III domain containing [protein] (FNDC5) [6]. Fibronectin type III domain-co[ntaining] protein consists of an extracellular region co[nta]ining the fibronectin type III (FnIII) domain, which is separated from a small cytoplasmic region by the h[ydro]phobic transmembrane segment and is proteolytically cleaved to irisin [10, 11]. [Fibro]nectin type III domains (FnIII) [are] monomeric consist of a combination of beta strands and ran[dom] coils (Figure 1). Irisin is a powerful messenger, sending [a] signal to determine the function of specific cells, like skeletal muscle, liver, pancreas, heart, fat and the brain [4-6].

2.1.2. Synthesis and Secretion

Synthesis and Secretion of Irisin are induced by exercise [via] peroxisome proliferator- activated receptor-γ (PPAR-γ) coactivator 1-α (PGC1α) [11]. Peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator is a multispecific transcriptional coactivator, capable of [activating] multiple genes in response to nutritional and physiological signal in tissues, where it is overexpressed,

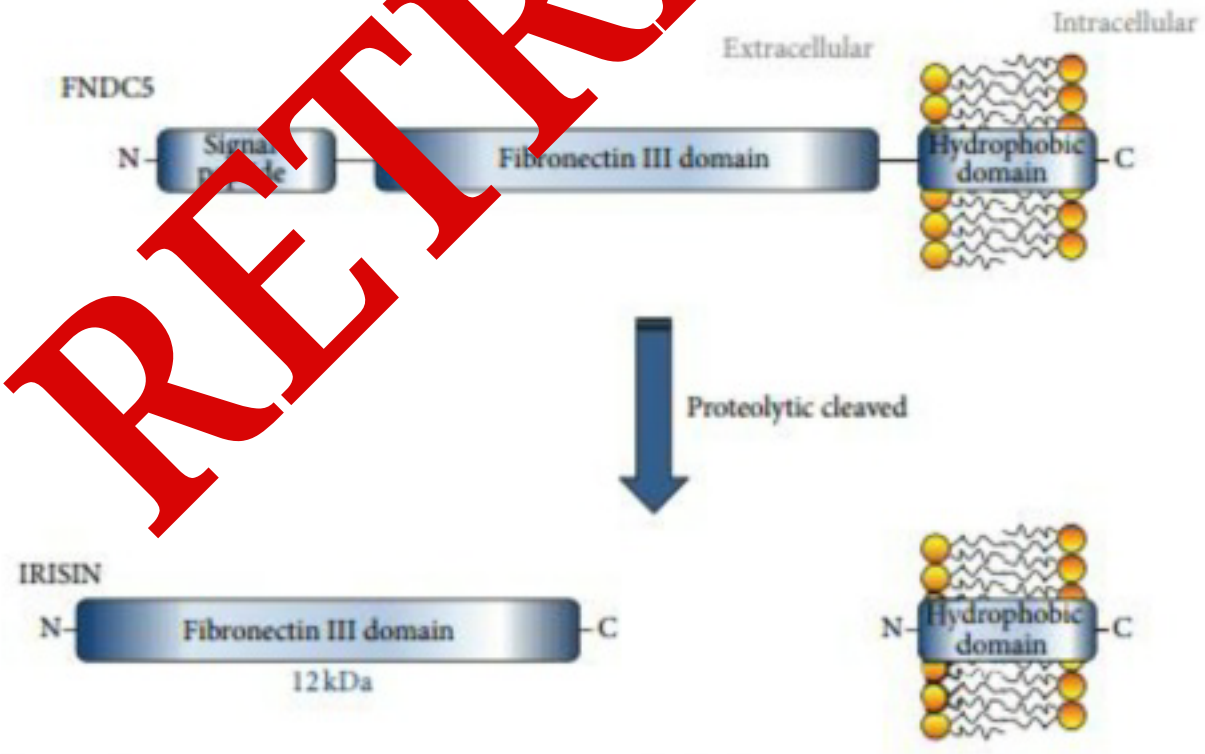

Figure 1 Structure of irisin

like skeletal muscle, brown adipose tissue, liver and heart [11-13]. Prolonged exercise increases the expression of PGC1α mainly in heart and skeletal muscle and then improves different metabolic parameters such as insulin sensitivity and signaling and also drives AMPK activation, phosphorylation of PGC1α, and FNDC5 production, followed by cleavage of FNDC5 to generate irisin (Figure 2) [11-13].

3. Mechanism of action

The most interesting things about irisin are its effects and potential applications but there is still some controversy surrounding the exact mechanism of irisin activity, specifically with respect to its expression and receptor. Many recent studies proposed that irisin is molecules released by skeleton and heart in response to exercise and act as messengers to tissues, including skeleton, heart, liver, fat and the brain [4, 6, 8, 9]. Many other very recent studies demonstrated that irisin exhibits therapeutic potential in insulin resistance and type2 diabetes mellitus by stimulating browning of white adipose tissue, promoting glucose uptake in skeletal muscle and heart, [illegible] hepatic glucose and lipid metabolism, and [illegible] function [2-5]. These and other many [illegible] logical functions of irisin can be accomplished through [illegible] activation of p38 mitogen activated protein [illegible] ase (p38 [illegible] PK) and extracellular regulated protein kinase (Figure [illegible] 15

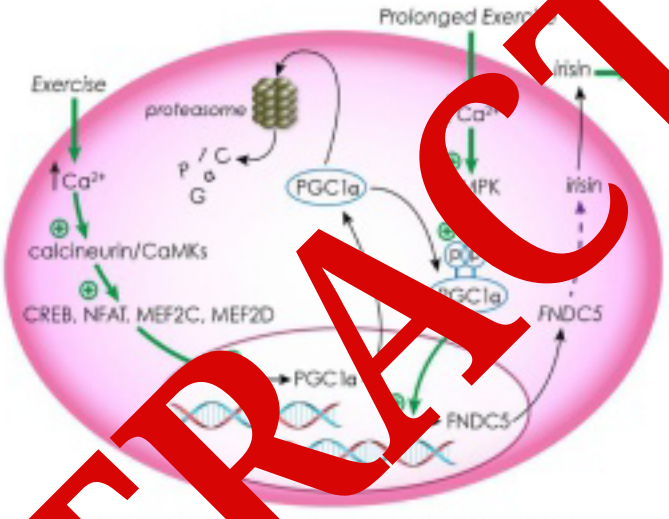

Figure 2 Mechanism [illegible] nesis and secretion of irisin

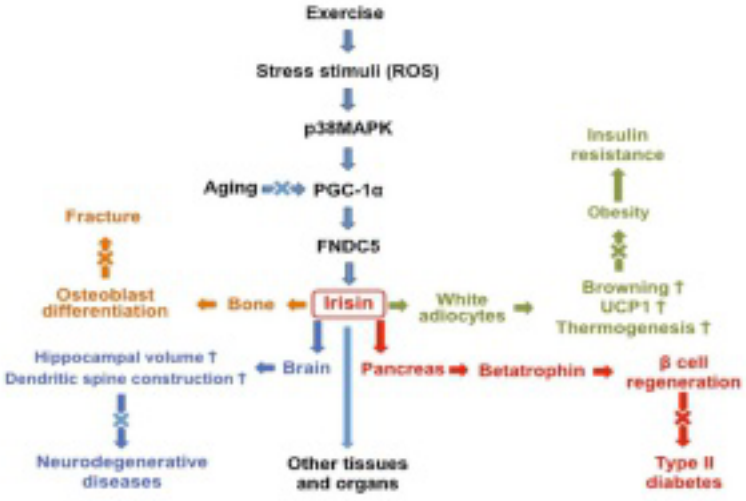

Figure 3 [illegible] nism of action of irisin on metabolism-associa[illegible]lth issues or metabolic diseases. '×' indica[illegible] the inhibition or blockage of signal pathways or diseases. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1-alpha; FNDC5, fibronectin domain-containing protein 5; UCP1, uncoupling protein 1; ROS, reactive oxygen species

4. Potential role of Irisin in insulin resistance and type 2 diabetes

Irisin can be secreted, activated and transported to a target on multiple tissues or organs for executing its corresponding physiological functions such as regulating white adipose tissue browning, improving energy consumption and glucose utilization, reducing insulin resistance, and synergistically treating metabolic diseases or metabolism-associated health issues such as obesity and type 2 diabetes (Figure 4) [15- 17].

4.1 Irisin and skeletal muscle

Skeletal muscle accounts for majority of glucose uptake in response to insulin and it is an important site of insulin resistance. Recent studies demonstrated that physical exercise induced the expression of peroxisome proliferator-activator receptor coactivator (PGC) 1 and its downstream membrane protein, fibronectin type III domain-containing 5 (FNDC5), which is cleaved to form irisin in skeletal muscle [18].

Together with the finding that FNDC5, the membrane protein that is cleaved to form irisin, is detected in skeletal muscle, indicates that a major site of irisin function may be skeletal muscle. Few experimental studies are tempting to speculate that irisin has the capacity to regulate glucose homeostasis in skeletal muscle systems in an autocrine manner [18, 19]. In addition, irisin activity was shown in vivo in very low concentration ranges, suggesting the existence of an irisin receptor in skeletal muscle and in many other body tissues. The crystal structure of the FNDC5 ectodomain was shown to correspond to irisin [19]. This implies that the irisin recepto[illegible]le irisin may work by binding to a receptor t[illegible] is yet to [illegible]enti-fied. The identity, the existence a[illegible]tion of ti[illegible]sin receptor have not been explored thus t[illegible]

Recent experimental studie[illegible]ved tha[illegible]in acti[illegible]es glucose uptake in the ske[illegible]tal muscles via [illegible]m [illegible]OS and P38 AMPK medi[illegible] AMPK pathway ([illegible]re 5). Therefore, irisin ha[illegible] bene[illegible]ect in s[illegible]elet[illegible] muscles via AMPK-related pa[illegible]way. In [illegible]mary, ir[illegible] was shown to stimulate gl[illegible]e uptake in s[illegible]l m[illegible]cle via AMPK2 activation m[illegible]ch[illegible]n likely involv[illegible]38 MAPK-GLUT4 translocati[illegible] [14, [illegible]These findi[illegible]s provide novel insights [illegible] the contri[illegible]n of irisin to glucose metabolis[illegible]n skeletal muscle [illegible]nd could potentially be co[illegible]e the focus of future re[illegible]arch on it into the treatment of [illegible]betes.

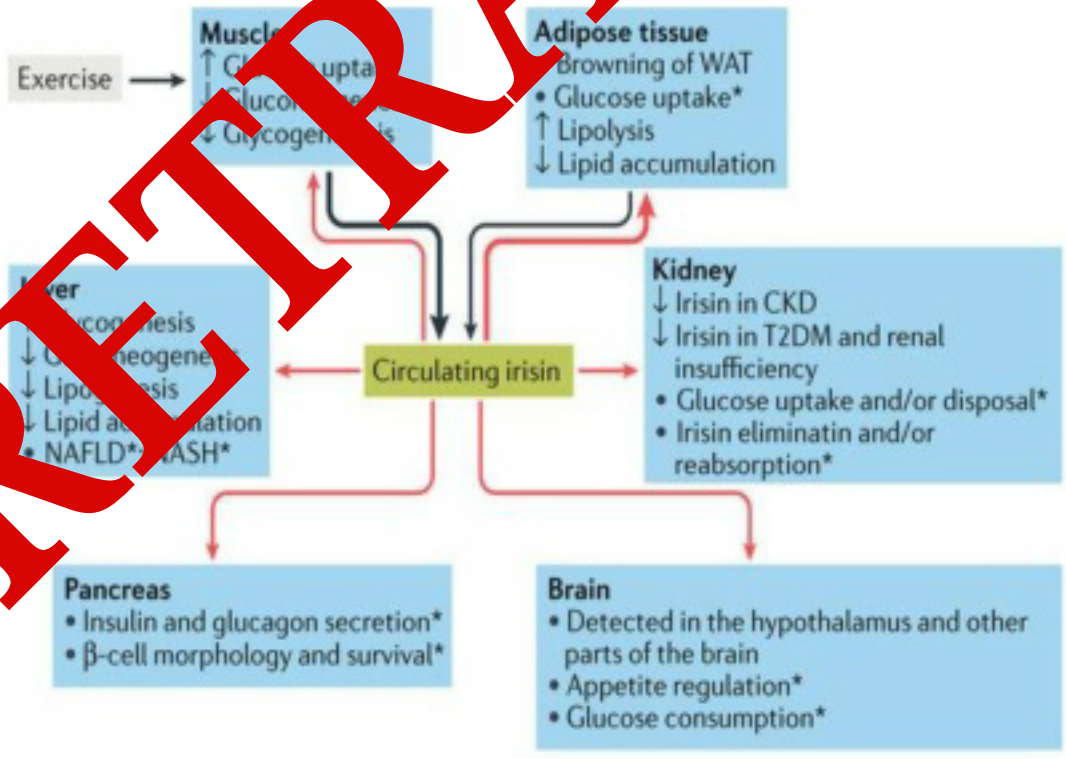

Figure 4 Potential roles of irisin

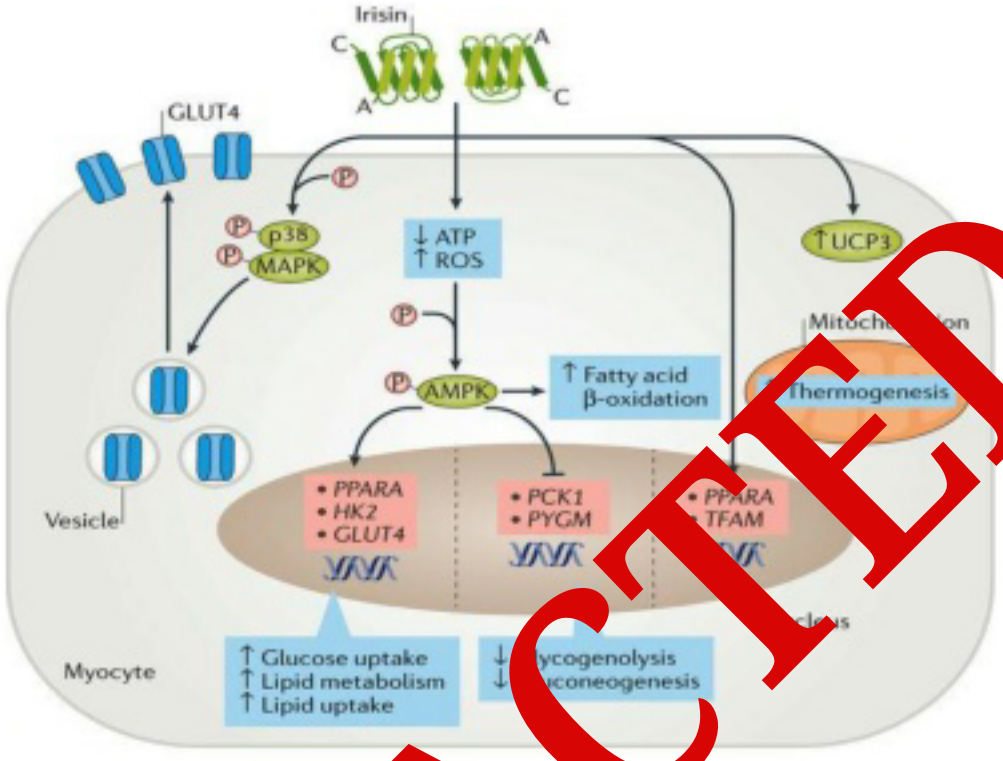

Figure 5 Physiological actions of irisi muscle

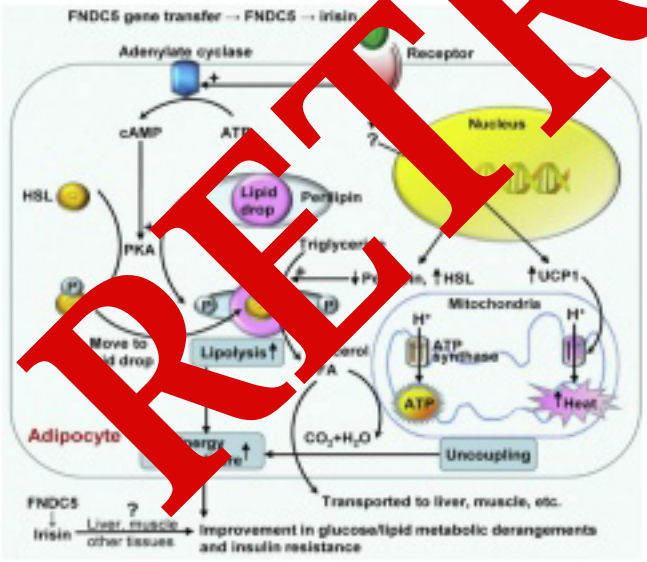

Figure 6 Effect of irisin on preventing glucose/lipid metabolic derangements, improves insulin resistance and increases energy expenditure via the enhanced lipolysis and the uncoupling of oxidative phosphorylation

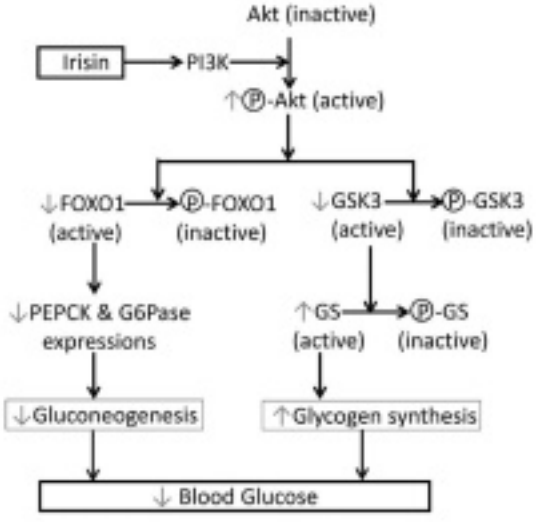

Figure 7 Underlying mechanisms of irisin on gluconeogenesis and glycogenesis in hepatocytes

4.2 Irisin and adipose tissue

The discovery of irisin and its potential to induce the browning of white adipocytes has gained much attention over the last 5 years. Adipose tissues play major roles in the energy homeostasis and in the development of obesity and metabolic syndrome, which may be a new target against obesity and metabolic disorders, such as insulin resistance and type 2 diabetes [20, 21]. Generally, adipose tissue includes two parts such as white adipose tissue (WAT), which functions as the dominant site for the storage of lipid, and brown adipose tissue (BAT), which functions as the thermogenesis through uncoupled respiration [20]. Adipocytes from WAT are the characteristics of unilocular lipid droplets, few mitochondria and relatively low metabolic rate; on the other hand, adipocytes from BAT are the characteristics of multilocular lipid droplets, plentiful mitochondria and relatively high metabolic rate [21].

Irisin induced browning of white adipocytes, which can be accomplished through the overexpression of UCP1 and metabolic improvement, which can be regulated through the activation of p38 mitogen activated protein kinase (p38 MAPK) and extracellular regulated protein kinase [14]. Irisin mainly acts on white adipose tissue and functions as the improved energy consumption, which can reduce high-fat-diet induced insulin resistance [20]. Current studies indicated that, irisin can also enhance lipolysis via cAMP-PKA-HSL/perilipin pathway (Figure 6) [24]. Generally, the conversion of white adipocytes to brown adipocytes leads to increase in energy expenditure and thermogenesis with subsequent improvement of insulin sensitivity, reductions in body weight, and improved glucose tolerance in mice [24-26].

4.3 Irisin and liver

Increased glucose production and reduced hepatic glycogen storage contribute to metabolic abnormalities in diabetes. Few studies in Europe tried to investigate the effect and underlying mechanisms of irisin on gluconeogenesis and glycogenesis in hepatocytes with insulin resistance and its therapeutic role in type 2 diabetic mice [27-30]. They proved that subcutaneous perfusion of irisin improved the insulin sensitivity, reduced fasting blood glucose, increased GSK3 and Akt phosphorylation, and suppressed GS phosphorylation, PEPCK and G6Pase expression in the liver. Generally, it improves glucose homoeostasis by reducing gluconeogenesis via PI3K/Akt/FOXO1-mediated PEPCK and G6Pase down-regulation and increasing glycogenesis via PI3K/Akt/GSK3- mediated GS activation (Figure 7). So, irisin may be regarded as a novel therapeutic strategy for insulin resistance and type 2 diabetes.

4.4 Irisin and β cell of pancreas

Current studies showed that irisin is insulin-regenerating hormone, and can specifically accelerate the generation of mouse beta cells and increase the number of mouse beta cells [31-33]. The regeneration of beta cells in human body will put forward a new avenue for the treatment of diabetes [32]. Based on these studies, a new hypothesis of signalling pathway, p38-PGC-1α -irisin beta cell signal pathway, is proposed. In this signal pathway, under the condition of muscle stimulation, the expression of PGC-1α reveals an obvious increase, thus correspondingly stimulating the expression and cleavage of FNDC5 to generate irisin, activating the expression of UCP1 in the presence of irisin, accelerating the browning of WAT, increasing energy consumption and promoting the regeneration of insulin, as well as stimulating the rebuilding of beta cells [34-35]. Generally, many experimental studies proved that irisin has anti-apoptotic actions on pancreatic beta-cells and stimulates beta-cell proliferation, insulin biosynthesis and secretion. The level of circulating irisin can improve glucose tolerance and reduce insulin resistance, which initiate a novel strategy for the treatment of diabetes (Figure 8) [34-36].

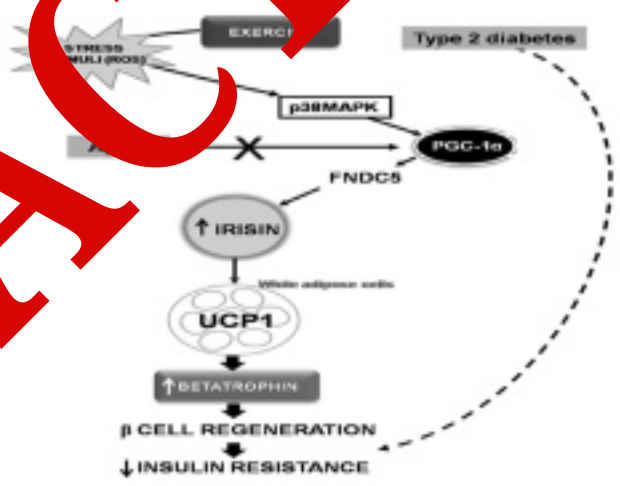

Figure 8 Irisin-betatrophin pathway and its possible implications in insulin resistance

4.5 Irisin and heart

The heart has tremendous energy requirements, both in physiological and pathological states, and a prominent feature of cardiovascular disease is myocardial metabolic dysregulation. Notably, pathological remodeling is associated with a switch from fatty acid metabolism, the primary energy source for the healthy adult human heart, to glucose utilization, which is the main energy source in fetal life. Improving metabolic dysfunctions of cardiac tissues is other very important for management of insulin resistance and type 2 diabetes [37].

Many studies suggested multiple functions of irisin. Strikingly, cardiac muscle expresses a high level of FNDC5 and after exercise produces more irisin than skeletal muscle [37]. The high level of irisin in cardiac muscle suggests its

potential but only few human studies explored its roles in cardiac function and performance [38-40]. However, the exact molecular mechanism by which irisin may have beneficial effect on cardiovascular system remains unknown.

Exercise training promotes efficient glucose and fatty acid handling, as well as mitochondrial biogenesis of heart via upregulation of the glucose sensor AMP activated kinase (AMPK) and its downstream target, the peroxisome proliferator activated receptor gamma coactivator 1α (PGC-1α) [41-43]. Whether irisin also contributes to the cardiac benefits of PGC-1α will be of great interest for future studies.

5. Conclusion

Irisin can be used as an effective strategy in attenuating metabolic derangements in insulin resistance and type 2 diabetes by stimulating browning of white adipose tissue, promoting glucose uptake in skeletal muscle and heart, improving hepatic glucose and lipid metabolism, and promoting pancreatic β cell function. So, Irisin is a novel and promising peptide hormone for insulin resistance and type 2 diabetes.

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