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

Mamo Gizaw\textsuperscript{1}, Pandi Anandakumar\textsuperscript{1*}, Tolessa Debela\textsuperscript{2}

\textsuperscript{1} Biochemistry Unit, Department of Biomedical Sciences, College of Health Sciences, Arsi University, Asella, Ethiopia
\textsuperscript{2} Physiology Unit, Department of Biomedical Sciences, College of Health Sciences, Arsi University, Asella, Ethiopia

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 liver. Since its discovery in 2012, it has been the subject of many researches due to its potent physiological role. It is believed that understanding irisin’s function 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 by 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 \( \beta \) 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.

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 prevalent\textsuperscript{1}. Insulin resistance and/or type 2 diabetes are characterized by a range of metabolic disturbances, such as hyperglycaemia, 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...
2. Biochemistry of irisin

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

2.1. 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 5 (FNDC5) [6]. Fibronectin type III domain-containing protein 5 consists of an extracellular region containing the fibronectin type III (FnIII) domain, which is separated from a small cytoplasmic region by the helical transmembrane section and is proteolytically cleaved to irisin [10, 11]. Fibronectin type III domains (FnIII) commonly consist of a combination of beta strands and random coils (Figure 1). 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 [4-6].

2.1.2. Synthesis and secretion

Synthesis and secretion of irisin are induced by exercise and peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator 1α (PGC1α) [11]. Peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator 1α is a multispecific transcriptional coactivator, capable of regulating multiple genes in response to nutritional and physiological signal in tissues, where it is overexpressed,
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, improving hepatic glucose and lipid metabolism, and pancreatic β cell function [2-5]. These and other many physiological functions of irisin can be accomplished through the activation of p38 mitogen activated protein kinase (p38 MAPK) and extracellular regulated protein kinase (Figure 3)[14, 15].

![Figure 2 Mechanism for synthesis and secretion of irisin](image)

![Figure 3 Mechanism of action of irisin on metabolism-associated health issues or metabolic diseases. ‘×’ indicates 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](image)
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 receptor and soluble irisin may work by binding to a receptor that is yet to be identified. The identity, the existence and function of the irisin receptor have not been explored thus far.

Recent experimental studies showed that irisin activates glucose uptake in the skeletal muscles via calcium/ROS and P38 AMPK mediated AMPK pathway (Figure 5). Therefore, irisin had beneficial effect in skeletal muscles via AMPK-related pathway. In summary, irisin was shown to stimulate glucose uptake in skeletal muscle via AMPK2 activation mechanism likely involving p38 MAPK-GLUT4 translocation [14, 15]. These findings provide novel insights into the contribution of irisin to glucose metabolism in skeletal muscle cells, and could potentially become the focus of future research on it into the treatment of diabetes.
**Figure 5** Physiological actions of irisin in skeletal 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 [20-23].

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 G5 phosphorylation, PEPCK and G6Pase expression in the liver. Generally, it improves glucose homeostasis by reducing gluconeogenesis via PI3K/Akt/FOXO1-mediated PEPCK and G6Pase down-regulation and increasing glycogenesis via PI3K/Akt/GSK3-mediated G5 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-UCP1 -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 completing 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. So, the level of circulating irisin can improve glucose tolerance and reduce insulin resistance, which can initiate a novel strategy for the treatment of diabetes (Figure 8) [34-36].

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.

References
1. Liu JJ, Wong MD, Toy WC, Tan CS, Liu S, Ng XW, et al. Lower circulating irisin is associated with type 2 diabetes mellitus. J Diabetes Complications 2013; 27(4):365-9.
2. Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE, Tsoukas MA, et al. CS. Circulating irisin in relation to insulin resistance and the metabolic syndrome. J Clin Endocrinol Metab. 2013; 98(12): 4899–907.
3. Park MJ, Kim D II, Choi JH, Heo YR, Park SH. New role of irisin in hepatocytes: The protective effect of irisin against hepatic steatosis in vitro. Cell Signal 2015; 27(9):1831–9.
4. Zhang Y, Li R, Meng Y, Li S, Donelan W, Zhao Y, Qi, et al. Irisin stimulates browning of white adipocytes through mitogen activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes 2014; 63(2):514-25.
5. Liu S, Du F, Li X, Wang M, Duan R, Zhang J, et al. Effects and underlying mechanisms of irisin on the proliferation and apoptosis of pancreatic β cells. PLoS One 2017; 12(4):e0175498.
6. Bostrom P, Wu J, Jedrychowski M-P, Korde A, Ye L, Lo J-C, et al. A PGC1-alpha dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012; 481: 463–8.
7. Kozakova M, Balkau B, Morizzo C. Physical activity, adiponectin, and cardiovascular structure and function. Heart Vessels 2013; 28(1): 91–100.
8. Chen N, Li Q, Liu J, Jia S. Irisin, an exercise-induced myokine as a metabolic regulator: an updated narrative review. Diabetes Metab Res Rev. 2016;32(1):51-9.
9. Roca-Rivada A, Castelao C, Senin LL. FNDC5/irisin is not only a myokine but also an adipokine. PLoS One 2013; 8(4): e50563.
10. Schumacher MA, Chinnam N, Ohashi T, Shah RS, Eriksson HP. The structure of irisin reveals a novel inter-subunit β-sheet fibronectin (FNIII) dimer: implications for receptor activation. J Biol Chem. 2013;22:288 (47):33738-44.
11. Norheim F, Langleite TM, Hjorth M, Holen T, Kielland A, Stadheim HK, et al. The effects of acute and chronic exercise on PGC-1alpha, irisin and browning of subcutaneous adipose tissue in humans. FEBS J. 2014; 281(3): 739–49.
12. Xu B. BDNF (I)rising from exercise. Cell Metab. 2013; 18(5): 612–4.
13. Moreno–Navarrete JM, Ortega F, Serrano M, Guerra E, Pardo G, Tinhonones F, et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. J Clin Endocrinol Metab. 2013; 98(4): 769–78.
14. Zhang Y, Li R, Meng Y, Li S, Donelan W, Zhao Y, et al. Irisin Stimulates Browning of White Adipocytes through Mitogen-Activated Protein Kinase p38 MAP Kinase and ERK MAP Kinase Signaling. Diabetes 2014;63(2):514-25.
15. Rizk FH, Elshweikh SA, Abd El-Naby AY. Irisin levels in relation to metabolic and liver functions in Egyptian patients with metabolic syndrome. Can J Physiol Pharmacol. 2016; 94(4):359-62.
16. Jung, UJ, Choi, MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci.2014; 15 (4): 6184–6223.
17. Liu JJ, Wong MD, Toy WC, Tan CS, Liu S, Ng XW, et al. Lower circulating irisin is associated with type 2 diabetes mellitus. J Diabetes Complications. 2013; 27(4):365–9.
18. Gouni-Berthold I, Berthold HK, Huh JY, Berman R, Spenrath N, Krone W, et al. Effects of lipid-lowering drugs on irisin in human subjects in vivo and in human skeletal muscle cells ex vivo. PLoS One 2013; 8:e72858.
19. Kurdyova T, Balaz M, Vician M, Maderova D, Vlcek M, Valkovic L, et al. Effects of obesity, diabetes and exercise on Fndc5 gene expression and irisin release in human skeletal muscle and adipose tissue: in vivo and in vitro studies. J Physiol. 2014; 592 (5):1091–107.
20. Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol. 2008; 9(5):367–77.
21. Castillo-Quan JI. From white to brown fat through exercise on PGC-1alpha, irisin and browning of subcutaneous adipose tissue. J Physiol. 2014;592(47):33738-44.
22. Castiljo-Quan JI. From white to brown fat through exercise on PGC-1alpha, irisin and browning of subcutaneous adipose tissue. J Physiol. 2014;592(47):33738-44.
25. Chen JQ, Huang YY, Gusdon AM, Qu S. Irisin: a new molecular marker and target in metabolic disorder. Lipids in Health and Disease 2015; 14(2): 1476-511.

26. Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdegue R, et al. FGF21 regulates PGC-1α and brown ing of white adipose tissues in adaptive thermogenesis. Genes Dev. 2012; 26: 271-81.

27. Liu JJ, Liu S, Wong MD, Tan CS, Tavintharan S, Sum CF, et al. Relationship between circulating irisin, renal function and body composition in type 2 diabetes. J Diabetes Complications 2014; 28(2):208–13.

28. Park KH, Zaichenko L, Brinkoetter M, Thankkar B, Shain-Efe A, Joung KE, et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. J Clin Endocrinol Metab. 2013; 98 (12):4899–907.

29. Tang H, Yu R, Liu S, Huwatibieke B, Li Z, et al. Irisin inhibits hepatic cholesterol synthesis via AMPK-SREBP2 signaling. EBioMedicine 2016;139-48.

30. Liu TY, Shi CX, Gao R, Sun HJ, Xiong XQ, Ding L, et al. Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes. Clin Sci(Lond). 2015; 129: 839–50.

31. Liu S, Du F, Li X, Wang M, Duan R Zhang J, et al. Effects and underlying mechanisms of irisin on the proliferation and apoptosis of pancreatic β cells. PLoS One.2017; 12(4):e0175498

32. Song H, Wu F, Zhang Y, Zhang Z, Wang F, Jiang M, et al. Irisin promotes human umbilical vein endothelial cell proliferation through the ERK signaling pathway and partly suppresses high glucose-induced apoptosis. PLoS One 2014; 9(10): e110273.

33. Moon HS, Dincer F, Mantzoros CS. Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines. Metabolism. 2013; 62(8): 1131-6.

34. Lu J, Xiang G, Liu M, Mei W, Xiang L, Dong J. Irisin protects against endothelial injury and ameliorates atherosclerosis in apolipoprotein E-Null diabetic mice. Atherosclerosis. 2015; 243(2):438-48.

35. Qiao X, Nie Y, Ma Y, Chen Y, Cheng R, Yin W, et al. Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways. Sci Rep. 2016; 6: 18732.

36. Zhu D, Wang H, Zhang J, Zhang X, Xin C, Zhang F, et al. Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses. J Mol cell Cardiol. 2015; 87: 138-147.

37. Adiposity and the metabolic syndrome. Peptides 2014; 52:68-73.

38. Qiao X, Nie Y, Ma Y, Chen Y, Cheng R, Yao Ying W. Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways. Sci Rep. 2016; 6: 18732.

39. Wu F, Song H, Zhang Y, Zhang Z, Mu Q, Jiang M, et al. Irisin Induces Angiogenesis in Human Umbilical Vein Endothelial Cells In Vitro and in Zebrafish Embryos In Vivo via Activation of the ERK Signaling Pathway. PLoS One. 2015; 10(8): e0134662.

40. Zhu D, Wang H, Zhang J, Zhang X, Xin C, Zhang F, et al. Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways. Sci Rep. 2016; 6: 18732.

41. Adiposity and the metabolic syndrome. Peptides 2014; 52:68-73.

42. Emanuele E, Minoretti P, Pareja-Galeano H, Sanchis-Gomar F, Garatachea N, Lucia A. Serum irisin levels, precocious myocardial infarction, and healthy exceptional longevity. Am J Med 2014; 127 (9):888–90.

43. Emanuele E, Minoretti P, Pareja-Galeano H, Sanchis-Gomar F, Garatachea N, Lucia A. Serum irisin levels, precocious myocardial infarction, and healthy exceptional longevity. Am J Med 2014; 127 (9):888–90.

44. Aronis KN, Moreno M, Polyzos SA, Moreno-Navarrete JM, Ricart W, Delgado E, et al. Circulating irisin levels and coronary heart disease: association with future acute coronary syndrome and major adverse cardiovascular events. Int J Obes (Lond) 2015; 39(1):156–61.