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Review Article

Irisin--New Hope for the Treatment of Diabetic Cardiomyopathy

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Abstract

Diabetic cardiomyopathy (DCM) as a diabetic cardiovascular complication, seriously affects the prognosis and quality of life of diabetic patients. Its pathological mechanism is complex, and myocardial fibrosis, disorders of glucose and lipid metabolism, insulin resistance, oxidative stress and inflammation are important factors involved, but there is still a lack of targeted therapeutic agents for the treatment of diabetic cardiomyopathy. As a new type of muscle factor, Irisin is mainly used to make white fat brown and increase the sensitivity of the body to insulin. In recent years, studies have confirmed that it plays an important regulatory function in cardiac remodelling and dysfunction, but it has not yet attracted much attention. Therefore, this paper provides an in-depth discussion on the role of Irisin in diabetic cardiomyopathy to help offer new ideas for the treatment of diabetic myocardial injury.

Keywords: diabetic cardiomyopathy; Irisin; myocardial fibrosis; oxidative stress

Clinical Report:

The global prevalence of diabetes has increased significantly. In 2019, there were about 463 million adults aged 20-79 years with diabetes worldwide, and it is expected to increase by 51% (to 700 million) by 2045 [1]. The rapid increase of diabetic patients is an important reason for the high incidence of diabetic cardiovascular disease. 44% of the deaths caused by type 1 diabetes mellitus (T1DM) and 65% of the deaths caused by type 2 diabetes mellitus (T2DM) were due to cardiovascular disease. DCM is one of the cardiovascular diseases of diabetes mellitus, which is closely related to the incidence of heart failure and mortality in diabetic patients. It causes myocardial metabolic disorders, myocardial fibrosis, diastolic and/or systolic dysfunction, and eventually develops into heart failure. At present, the pathogenesis of DCM is not fully understood, and there is a lack of specific molecular markers and therapeutic targets. Irisin is a new muscle factor, which is highly expressed in the myocardium. In recent years, more and more studies have shown that Irisin is closely related to DCM, but the exact molecular mechanism of Irisin in DCM is still unclear. This article briefly reviews the effect and mechanism of Irisin on diabetic cardiomyopathy, so as to provide new ideas for clinical treatment of diabetic cardiomyopathy.

1. Irisin

Irisin is a new muscle factor discovered by BOSTROM in 2012[2] . Exercise can promote peroxisome proliferator-activated coactivator-1α (PPARγ coactivator-1α, PPARγ coactivator-1α, PPARγ coactivator-1α) in skeletal muscle. PGC-1α) and its downstream protein fibronectin type III domain-containing protein 5 (FNDC5) were expressed. The extracellular part of FNDC5 was cleaved and modified to form a secreted protein called Irisin. Studies have found that[2], Irisin is contained in skeletal muscle and myocardium of mice, and is also expressed in plasma, adipose tissue, brain tissue, liver and kidney. Such a wide expression indicates that Irisin may have important physiological functions.

The primary and most basic physiological function of Irisin is to increase the expression of uncoupling protein 1 (UCP-1) through the p38-MAPK/ERK pathway, so as to transform white fats (WAT) into brown fats (BAT) which can catabolize fat [2]. Another important physiological function is the regulation of glucose metabolism. Irisin can inhibit the apoptosis of islet β cells and improve the function of islet β cells by increasing the expression of pro-apoptotic genes Caspases, Bad and Bax and decreasing the expression of anti-apoptotic genes Bcl-2 and Bcl-xl [3]. In addition, Irisin has other biological effects. In the nervous system, Irisin plays a neuroprotective role by activating AKT and ERK1/2 signaling pathways in brain tissue [4], increasing the expression of brain-derived neurotrophic factor (BDNF). During exercise, FNDC5 is highly expressed in the myocardium, and the myocardium produces more Irisin than skeletal muscle [2,5], suggesting its potential role in cardiac function and performance. In addition, Irisin can affect the physiological function of bone marrow by acting on ERK, P13K/AKT and BMP2 signals in bone marrow mesenchymal stem cells, p38MAPK and AMPK signals in osteoblasts, ERK signals in osteocytes, RANK/RANKL signals in osteoclasts and NF-KB signals in chondrocytes [6]. In summary, Irisin is involved in the occurrence and development of a variety of diseases, including inflammation, aging, neurodegenerative diseases and other metabolic diseases. Based on its various physiological effects, Irisin is expected to become a target for the prevention and treatment of metabolic diseases and other diseases.

2. Diabetic cardiomyopathy

Diabetic cardiomyopathy, first described in 1972, is a specific type of cardiomyopathy after excluding other cardiovascular diseases such as hypertension, coronary heart disease, valvular disease, and congenital heart disease [7-9], which is one of the cardiovascular complications of diabetes. Studies have found that the common pathophysiological mechanisms include insulin resistance and/or deficiency, calcium ion (Ca2+) imbalance in cardiomyocytes, mitochondrial damage, oxidative stress, and inflammatory response.

Hyperglycemia caused by insulin deficiency and/or insulin resistance is the starting point of the cascade of cardiac dysfunction in DCM [10]. Insulin resistance can increase the uptake of free fatty acid (FFA) in cardiomyocytes and further aggravate mitochondrial fatty acid β-oxidation damage. Results in mitochondrial dysfunction and accumulation of lipotoxic metabolites. Mitochondrial dysfunction, Ca2+ imbalance and endoplasmic reticulum stress interact with each other to promote the occurrence and development of DCM. Among them, Ca2+ imbalance plays an important role in the occurrence of heart failure in diabetic cardiomyopathy[11]. In the hyperglycemia environment, a large number of reactive oxygen species (ROS) cause abnormal protein translation and folding, leading to abnormal DNA expression, which causes cell damage and endoplasmic reticulum stress. Under the joint action of the two, mitochondria induce apoptosis by increasing the permeability of the outer membrane, leading to the rapid entry of solutes and water into the mitochondrial matrix, resulting in ATP synthesis disorder. Excessive uptake of Ca2+ by mitochondria causes Ca2+ overload, which damages mitochondrial function[12] and leads to heart failure [13]. In addition, the accumulation of angiotensin Ⅱ (Ang Ⅱ), advanced glycation end products, and lipotoxicity can promote cardiomyocyte hypertrophy and extracellular matrix remodeling, resulting in microcirculation damage, affecting myocardial energy supply, and ultimately developing heart failure. In conclusion, the pathogenesis of diabetic cardiomyopathy is complex and needs to be further studied.

3. The protective effect and mechanism of Irisin on diabetic cardiomyopathy

3.1 Improvement of myocardial fibrosis

Myocardial fibrosis is a characteristic pathological change of DCM and an important cause of irreversible heart failure. Oxidative stress and activation of renin-angiotensin-aldosterone system (RAAS) play an important role in the occurrence and development of myocardial fibrosis in DCM.

3.1.1 Inhibition of angiotensin Ⅱ improves myocardial fibrosis

In the state of high glucose, the activity of local sympathetic nerve in myocardium increases, thereby activating the RAAS system [14], causing increased heart rate and peripheral vascular constriction, leading to ventricular stiffness. Ang Ⅱ, the main active peptide of RAAS, was found in an animal study [15], and AngII was also involved in the process of cardiomyopathy in the early stage of diabetes.

Previous studies have shown [16] that the TGFβ pathway is at the center of the fibrotic response, and AngII can directly activate the TGFβ pathway or indirectly induce this pathway through oxidative stress, leading to myocardial fibrosis. Liu [17] et al. found that low dose (0.5μg/g) Irisin could directly inhibit AngII-induced fibrosis in vitro and in vivo and could also reduce cardiac fibrosis by inhibiting redox-sensitive TGFβ1-Smad 3 signaling. At present, the optimal dose of Irisin to inhibit AngII and TGFβ pathways has not been solved, and further studies are needed to verify it.

3.1.2 Anti-oxidative stress inhibits myocardial fibrosis

Oxidative stress is a state of dynamic imbalance between the oxidative system and the antioxidant system of the body, which is a negative effect caused by free radicals in the body, and is closely related to aging and diseases. nuclear factorerythroid2-related factor 2 (Nrf2), as a key transcription factor of cellular antioxidant defense system, plays an important role in anti-chemical stress [18]. In recent years, Nrf2 has also been shown to have anti-fibrosis effects [19].

ZHANG et al. [20] found that Irisin blocked the downregulation of Nrf2 and retained its transcriptional activity in cardiomyocytes with injury, and the protein level of Nrf2 in the nucleus increased with the increase of Irisin. Since the mRNA level of Nrf2 was also unchanged, it is speculated that Irisin may inhibit nuclear export and degradation of Nrf2. Previous studies [21,22] have identified that AKT/GSK3β/FYN signaling pathway can activate Nrf2 transcriptional activity. ZHANG[20]et al. treated H9C2 cells with

irigenin and found that GSK3β inactivation reduced FYN phosphorylation, and then reduced Nrf2 nuclear export and degradation. These data confirm that Irisin mediates the AKT/GSK3β/FYN/Nrf2 signaling pathway to play a role in anti-fibrosis and anti-oxidative stress in cells, but the specific mechanism of Irisin regulating Nrf2 remains to be elucidated.

3.2 Inhibition of inflammation

Activation of proinflammatory immune cells has also been implicated in DCM [23]. Proinflammatory cytokines, such as IL-6, TNF-α and MCP-1, lead to myocardial oxidative stress and coronary artery dysfunction [9].After Irisin intervention, the above inflammatory factors were significantly decreased, suggesting that Irisin may alleviate myocardial inflammatory injury by inhibiting the secretion of inflammatory factors. Thus slowing down the development of DCM.

NFκB is a protein complex that regulates DNA transcription and the expression of inflammatory factors [23]. In DCM model, activated NFκB can promote the expression of inflammatory factors (TNFα, IL-4, IL-6), and inhibit the rapid degradation of IκBα protein, activate NFκB signaling pathway, and cause myocardial inflammatory injury. It eventually leads to myocardial damage [24].

Studies have found that exogenous administration of Irisin can significantly inhibit the expression of inflammatory factors such as IL-1β, IL-6 and TNF-α, which may play a role through NFκB pathway [25]. Based on the above results, Zhang Chi et al. [26] detected NFκB related protein levels in the nucleus and cytoplasm and found that: The expression of NFκBp65 was increased in the nucleus and decreased in the cytoplasm of the DCM group and the high glucose/high-fat group, and the expression of IκBα was inhibited. After treatment with NFκB inhibitor or Irisin, the above phenomenon was partially reversed, suggesting that Irisin may reduce the expression of inflammatory factors by inhibiting NFκBp65 from nucleus. Finally, it can alleviate myocardial inflammatory injury.

3.3 Improve mitochondrial function

Abnormal glucose and lipid metabolism can cause cardiomyocytes to over-rely on fatty acid β-oxidation for energy, which increases mitochondrial oxygen consumption rate, causes damage to the respiratory chain, and generates excessive peroxides and reactive oxygen species (ROS) [27]. ROS overload will promote the opening of mitochondrial permeability transition pore (MPTP) in the mitochondrial inner membrane, leading to membrane potential depolarization, reverse transport of ATP synthase, and eventually leading to cell energy depletion and cardiomyocyte death [28].

Studies have shown [29] that Irisin can prevent myocardial ischemia-reperfusion (MI/R) injury, which is related to the improvement of mitochondrial function. Wang [30] et al. found that Irisin inhibited mitochondrial MPTP opening by increasing superoxide dismutase 1 (SOD1) expression and p38 phosphorylation, thereby alleviating mitochondrial dysfunction. Inhibiting the opening of MPTP can protect the heart from myocardial cell damage caused by ischemia/reperfusion [31]. In addition, Lu et al. [32] found that, Irisin inhibits phosphorylated endoribonuclease inositol-requiring enzyme 1α via a mitochondrial ubiquitin ligase-dependent mechanism. IRE1α), glucose regulated protein 78(GRP78), C/EBP homologous protein (CHOP) and other ER stress-related proteins. Promoting the expression of mitochondrial electron transport chain complex to alleviate MI/R injury in mice. PGC-1α is a major regulator of mitochondrial synthesis. In the cardiovascular system, PGC-1α signaling pathway regulates mitochondrial production to maintain and repair mitochondrial function in cardiovascular system cells such as cardiomyocytes and vascular endothelial cells. Studies have shown that [33] Irisin directly binds to the endothelial cell surface receptor integrin αV/β5, thereby phosphorylating AMPK (Thr 172) and activating PGC-1α and mitochondrial transcription factor A (the key activator of mitochondrial transcription), stimulating a large number of mitochondria and protecting mitochondrial function.

3.4 Regulation of intracellular Ca2+ levels in cardiomyocytes

Calcium ion is closely related to the action potential of cardiomyocytes, which is an important factor affecting the systolic and diastolic function of the ventricle. Calcium-triggered calcium release plays an important role in the excitation-contraction coupling of cardiomyocytes. The sarcoplasmic reticulum of cardiomyocytes is underdeveloped and the storage of Ca2+ is small, so it needs to use the Ca2+ influx through L-type calcium channel in the plateau phase to trigger the sarcoplasmic reticulum to release a large amount of Ca2+ to achieve the Ca2+ concentration required to trigger myocardial contraction.

XIE [34] et al. performed real-time Ca2+ imaging analysis in H9C2 cells by stimulating cardiomyocytes with different concentrations of recombinant Irisin and found that recombinant Irisin increased Ca2+ concentration several-fold. Studies have found that the opening of L-type Ca2+ channels is dependent on the activation of the PI3K/AKT pathway [35], a serine/threonine protein kinase that plays an important regulatory role during cardiac development. XIE [34] et al. treated H9C2 cells with recombinant Irisin (50nM) for 5, 20 and 30 minutes, and observed that AKT phosphorylation began at 5 minutes and peaked at 20 minutes. In addition, PI3K-AKT signaling pathway was activated after injection of recombinant Irisin into mice. These data suggest that Irisin is involved in cardiac development, remodeling and metabolism by activating PI3K-AKT signaling pathway.

3.5 Regulation of glucose and lipid metabolism

Lipogenesis and insulin resistance are closely related to metabolic diseases. Hyperlipidemia and hyperinsulinemia promote the transfer of fatty acids into cardiomyocytes, and lipotoxicity will occur when the oxidation ability of fatty acids is not sufficient [36], resulting in the increase of ceramide and ROS production, inhibition of mitochondrial respiratory chain to induce apoptosis of cardiomyocytes, and the opening of K+ channels. It reduces the action potential time and opens L-type calcium channel, which affects the uptake of calcium by sarcoplasmic reticulum calcium pump and impairs the contractile function of myocardium.

Activation of AMPK can regulate glucose and fat metabolism, attenuate lipogenesis and gluconeogenesis, promote lipid oxidation and glycolysis, and have anti-diabetic effects in the liver. Irisin has been found to be involved in the AMPK activation pathway [37] and promote AMPK downstream signaling systems. Thus, it can up-regulate the expression of genes that promote glucose and lipid catabolism such as PPARα, HK2, GLUT4, and down-regulate the expression of genes that promote glucose production such as PCK1, muscletype glycogen phosphorylase (PYGM), G6PC, and play a hypoglycemic and lipid-regulating role. In addition to the above pathways, Irisin can also promote subcutaneous adipose thermogenesis by stimulating the expression of UCP-1, which converts WAT into BAT. Studies have shown[38] that enhanced

BAT thermogenesis improves glucose tolerance, increases insulin sensitivity, and decreases body weight and fat mass. However, in addition to accelerating lipololysis, reducing hepatic gluconeogenesis, and reducing insulin resistance, Irisin also inhibits hepatic cholesterol synthesis through AMPK-cholesterol regulatory element binding protein-2 (SREBP2) signaling axis [39]. It can also increase bile cholesterol transport and fecal cholesterol excretion by upregulating the expression of adenosine triphosphate binding transporter G5/G8(ABCG5/G8) in liver and intestinal cells [40], thereby reducing triglyceride, total cholesterol, and low-density lipoprotein cholesterol levels in obese or diabetic mice. In conclusion, Irisin plays an important role in regulating glucose and lipid metabolism.

4. The therapeutic prospect of Irisin in DCM

The pathogenesis of DCM is complex, and there is no specific diagnosis and treatment method. Poor blood glucose control is closely related to the occurrence of heart failure, so hypoglycemic drugs have a certain protective effect on the heart.

As a widely used hypoglycemic drug, metformin can reduce the remodeling of cardiomyocytes and fibroblasts, promote the production of NO, and improve the systolic and diastolic functions of the heart by reducing insulin resistance and TNF-α expression [41]. Studies have found that metformin can up-regulate the expression of Irisin by activating AMPK/SIRT1/PGC-1α signaling pathway and play a protective role on islet β cells [42]. However, to date, there is no specific regulator of Irisin, and further in-depth studies are needed to find it. Glucagon-like peptide 1 (GLP1) receptor agonists can increase insulin secretion and reduce glucagon, thereby reducing myocardial ischemia/reperfusion injury and left ventricular remodeling, while increasing the expression of NO and improving vascular endothelial function, thus protecting the heart [43]. Similar to GLP-1, Irisin can promote the production and secretion of insulin and improve the

proliferation and survival of β cells by activating the same intracellular signaling molecules, such as AKT, CREB and ERK1/2 [44]. In addition, compared with traditional insulin injection, Irisin can not only reduce blood glucose, but also inhibit fat deposition in the body and play a role in weight control. However, the half-life of Irisin in the body is short, so the study of Irisin receptor is particularly special. Irisin analogues can be developed through its receptor to replace Irisin, so as to avoid the shortcomings of the short half-life of Irisin and make it play a better role. With the deepening of research on Irisin and clinical drugs, the research progress of Irisin in clinical application has been accelerated, and it has opened up a new path for the diagnosis and treatment of DCM.

Conclusion and Prospect

DCM is a major cardiovascular-related complication in diabetic patients. At present, there is still a lack of biomarkers with high specificity and sensitivity, and there is also a lack of specific and effective clinical diagnosis and treatment methods. Irisin may delay the progression of DCM by inhibiting myocardial fibrosis, inhibiting inflammation, improving mitochondrial function, regulating intracellular Ca2+ level, regulating glucose and lipid metabolism and accumulation. Irisin is expected to become a biomarker and therapeutic target for DCM. At present, the research on the role and mechanism of Irisin in DCM is still in the stage of in vivo cell or in vitro mouse experiments, and the specific mechanism of its action in human is not clear. Therefore, our future research should focus on the above issues at the molecular level and clinical research, in order to provide theoretical basis and practical guidance for the use of Irisin in the prevention and treatment of metabolic diseases.

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