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CONTEMPORARY REVIEW

The Emerging Role of Irisin in Cardiovascular Diseases

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ABSTRACT: Irisin, a novel hormone like polypeptide, is cleaved and secreted by an unknown protease from a membrane-spanning protein, FNDC5 (fibronectin type III domain-containing protein 5). The current knowledge on the biological functions of irisin includes browning white adipose tissue, regulating insulin use, and anti-inflammatory and antioxidative properties. Dysfunction of irisin has shown to be involved in cardiovascular diseases such as hypertension, coronary artery disease, myocardial infarction, and myocardial ischemia–reperfusion injury. Moreover, irisin gene variants are also associated with cardiovascular diseases. In this review, we discuss the current knowledge on irisin-mediated regulatory mechanisms and their roles in the pathogenesis of cardiovascular diseases.

Key Words: cardiovascular diseases ■ exercise ■ irisin ■ vascular function

Cardiovascular diseases (CVDs), including coronary heart disease, hypertension, heart failure, and stroke, are the leading causes of morbidity and mortality in the world, accounting for nearly 30% of the total deaths worldwide.[1] According to the 2018 report on CVDs in China, it was estimated that about 290 million patients suffer from CVDs and CVD-related deaths.[2] Thus, increasing the efficacy in preventing and controlling CVDs is expected to have huge potential in decreasing healthcare costs and improving global health.

Exercise is an effective method to improve CVDs.[3,4] Regular exercise affects not only the metabolism of skeletal muscle, but also other organs such as the heart, liver, and visceral adipose tissue.[5] One of potential mechanisms underlying this crosstalk is the secretion of some peptides classified as myokines, which mediate communication between muscle and other tissues through endocrine mechanisms.[6,7] In the past few decades, studies have found that exercise exerts beneficial effects on CVDs via secreting several myokines such as myostatin,[8] FGF21 (fibroblast growth factor 21),[9] and BDNF (brain-derived neurotrophic factor).[10]

In 2012, Bostrom and colleagues first proposed that irisin was a muscle-derived energy expenditure signal by promotion of browning white adipose tissue through increasing the expression of UCP-1 (uncoupling protein 1).[11] Further studies have shown that irisin exerts beneficial effects such as anti-inflammation[12] and antioxidation,[13] regulating insulin synthesis and use,[14,15] and improving glucose and lipid metabolism.[16] The perturbation of those processes and/or deficiency of irisin causes impaired metabolic responses, which then lead to CVDs. In this review, we discuss our evolving understanding of the role of irisin in CVDs, summarize the current knowledge of irisin-mediated regulatory mechanisms, and highlight the therapeutic potential of irisin against CVDs.

BASIC CHARACTERISTICS OF IRISIN

Origination and Distribution

Irisin, a peptide of 112 amino acids, is a PGC-1α (proliferator-activated receptor-γ coactivator-1α)-dependent myokine, and is cleaved from FNDC5

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Nonstandard Abbreviations and Acronyms

ADAM	disintegrin and metalloproteinase
AMPK	adenosine monophosphate-activated protein kinase
BNDF	brain-derived neurotrophic factor
DRP1	dynamin-related protein
ERK	extracellular regulated protein kinase
FGF21	fibroblast growth factor 21
FNDC5	fibronectin type III domain-containing protein 5
GPX-1	glutathione peroxidase 1
HDAC4	histone deacetylase 4
HO-1	heme-oxygenase 1
ICAM-1	intercellular adhesion molecule-1
IL-1β	interleukin-1β
MAPK	p38 mitogen-activated protein kinase
MCP-1	macrophage chemotactic protein-1
MI/R	myocardial ischemia–reperfusion
MITOL	mitochondrial ubiquitin ligase
mTOR	mammalian target of the rapamycin
NADPH	nicotinamide adenine dinucleotide phosphate
NF-κB	nuclear factor-κB
NLRP3	leucine-rich repeat containing family pyrin domain containing 3
Nrf2	nuclear factor E2-related factor 2
PGC-1α	proliferator-activated receptor-γ coactivator-1α
PKA	protein kinase A
PKC-β	protein kinase C-β
PPARα	peroxisome proliferation-activated receptor α
SOD	superoxide dismutase
TGF-β1	transforming growth factor β1
TNF-α	tumor necrosis factor-α
TRPV4	transient receptor potential vanilloid 4
UCP-1	uncoupling protein 1
VCAM-1	vascular cell adhesion molecule-1

(fibronectin type III domain-containing protein 5), a membrane-spanning protein.[17] The FNDC5 protein is composed of an N-terminal signal sequence, a fibronectin type III domain, an unidentified region, a transmembrane domain, and a C-terminal part.[18] The C-terminal fragment of FNDC5 is located in the cytoplasm, whereas the extracellular N-terminal portion is proteolytically cleaved to produce irisin.[19] Irisin has a 100% similarity between mice and humans.[20] One study reported that FNDC5 is cleaved into irisin, at least partially, in an ADAM (disintegrin and metalloproteinase) family-dependent manner.[21]

The *Fndc5* gene is highly expressed in organs containing muscles such as skeletal muscle, heart, vascular, and rectum. In mice, muscle-derived irisin represents ~72% of the total circulating levels of this protein; the remaining 28% probably derives from adipose tissue and other organs such as the liver, kidney, brain, and pancreas.[17,22] Strikingly, cardiac muscle expresses a high level of FNDC5, and exercise produces more irisin in cardiac muscle than skeletal muscle.[23] These suggest its potential roles in cardiac function and performance.

Regulation of Irisin

Role of Exercise

The synthesis and the release of irisin are mainly regulated by exercise[19] and cold-induced shivering.[24] However, it should be noted that the existence of circulating irisin in humans and whether this hormone can be secreted after exercise were once controversial because of doubts surrounding the adenine thymine adenine translation start codon in human FDNC5, the reliability of irisin antibodies, and commercial irisin ELISA kits.[25–27] However, a study by Jedrychowski et al has put this controversy to rest by confirming the presence of irisin in human plasma and its elevation after exercise using quantitative mass spectrometry.[28] The levels of circulating irisin in healthy humans are in the 3 to 5 ng/mL range, which are increased after exercise.[29–31] Moreover, the duration of exercise is important for changes in circulating levels of irisin. Investigators have found that levels of irisin peak after 3 to 60 minutes of exercise and return to baseline 6 hours later, but chronic exercise (ranging from 6 weeks to 1 year) did not alter circulating levels of irisin, indicating that acute, but not chronic exercise triggers irisin release from muscle.[32,33] Moreover, the type of acute exercise also affects irisin. Studies suggested that resistance exercises as well as heavy strength training, but not endurance exercises, stimulated the increase in irisin serum levels.[33,34] Mechanically, exercise stimulates FNDC5 expression and increases serum irisin through activating AMPK (adenosine monophosphate-activated protein kinase) or MAPK (p38 mitogen-activated protein kinase)–PGC-1α pathway.[35–37] In addition, the deprivation of muscle intracellular ATP after exercise might trigger the synthesis of FNDC5 and the release of irisin.[38] In addition, Lee et al found that cold exposure through shivering-related muscle contraction could lead to increased circulating levels of irisin. Their work showed an induction of irisin secretion proportional to shivering intensity, in magnitude similar to exercise-stimulated secretion.[39]

Other Factors

Studies have shown that synthesis of FNDC5 and release of irisin are negatively regulated by fatty

acids and high glucose. In vitro studies showed that saturated fatty acid palmitate[40] or high glucose[41] inhibited FNDC5 mRNA and protein expression in a concentration-dependent manner. In addition, FNDC5 expression was moderated by inflammatory factors. For example, incubation of myotubes with IL-1β (interleukin-1β) or TNF-α (tumor necrosis factor-α), or both, reduces FNDC5 protein synthesis[42] (Figure 1).

IRISIN AND CARDIOVASCULAR RISK FACTORS

The effects of irisin on lipid accumulation and glucose homeostasis in skeletal muscle, the liver, and adipose tissue have been well discussed by other researchers.[43,44] In our present article, we will focus on the relationship between irisin and cardiovascular risk factors from the following 4 aspects.

Browning of White Fat

Mammals have 2 types of adipose tissue: white and brown. Brown adipose tissue has numerous mitochondria and is specialized to uncouple mitochondrial respiration, allowing for the generation of heat.[45] Böstrom et al first found that irisin activated oxygen consumption and thermogenesis in cultured white adipocytes, and injection of an adenoviral vector expressing irisin into mice resulted in browning of subcutaneous white fat.[17] Similarly, Xiong et al found that *Fndc5* mutation attenuated exercise-induced browning of white adipose tissue in mice.[46] In vitro studies also showed that irisin could robustly induce a brown fat gene program, such as *Ucp1*, in cultured white adipose cells.[47]

The underlying mechanisms of irisin-induced white fat browning are complex. Boström et al found that irisin-mediated increased UCP1 expression could be abolished by inhibition of the PPARα (peroxisome proliferation-activated receptor α), and they proposed that PPARα may act downstream of irisin to promote the fat browning program.[17] A study also showed that an irisin-induced browning effect was probably triggered by irisin-mediated activation of the ERK (extracellular regulated protein kinase)–p38MAPK signaling pathway because the upregulated UCP-1 expression was abolished by inhibition of the p38MAPK and

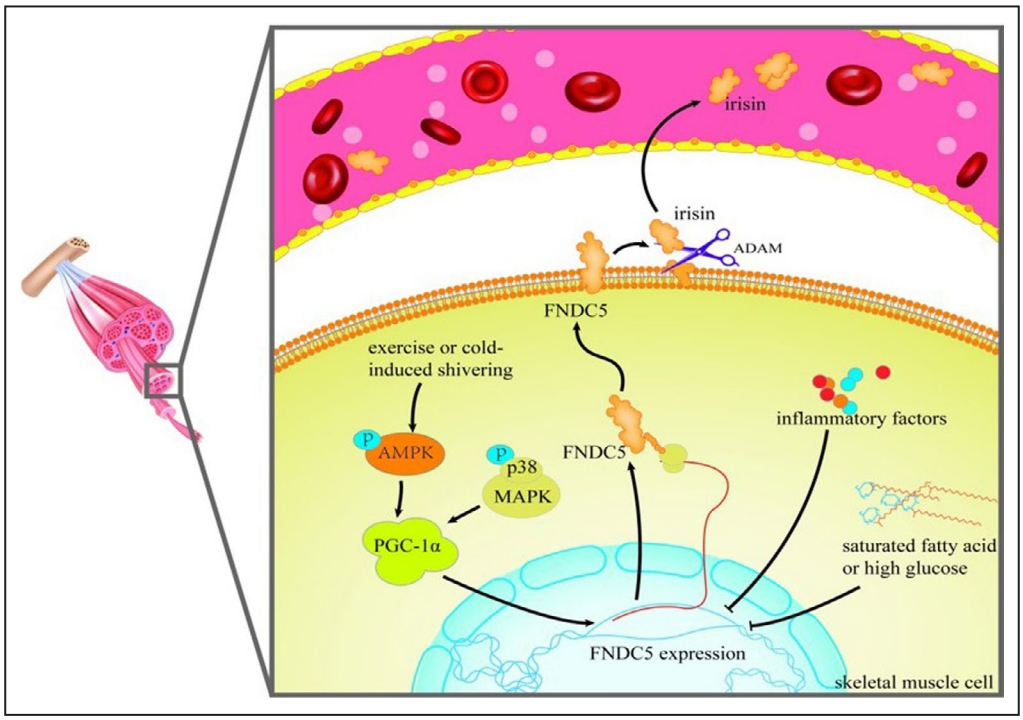

Figure 1. Exercise and cold-induced shivering induce PGC-1α expression in skeletal muscle through stimulating AMPK and p38MAPK signaling pathways.
Upregulated PGC-1α expression in turn drives the production of membrane protein FNDC5. However, inflammatory factors, high glucose, and saturated fatty acid suppress FNDC5 expression. The FNDC5 is cleaved by ADAM and then secretes irisin into the blood circulation. ADAM indicates disintegrin and metalloproteinase; AMPK, adenosine monophosphate-activated protein kinase; FNDC5, fibronectin type III domain containing protein 5; MAPK, mitogen-activated protein kinase; and PGC-1α, proliferator-activated receptor-γ coactivator-1α.

ERK.[48] Moreover, a recent study demonstrated that irisin induced the upregulation of brown fat-specific proteins, such as HO-1 (heme-oxygenase 1), cytosolic p62, and Nrf2 (nuclear factor E2-related factor 2) in adipocytes, and the browning effects of irisin were attenuated by treatment with HO-1inhibitor SnPP or p62 siRNA, suggesting that the irisin-induced browning effect may be via the p62/Nrf2/HO-1 signaling pathway.[49]

Irisin and Inflammation

Irisin expression has been shown to be positively correlated with anti-inflammatory factor IL-10 and negatively correlated with TNF-α levels.[50] Treatment with irisin suppresses the expression of proinflammatory cytokines such as NF-κB (nuclear factor-κB), ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1), TNF-α, IL-6,[51,52] and reduces MCP-1 (macrophage chemotactic protein-1) expression, which subsequently attenuates migration of macrophages.[53]In addition, irisin could induce the phenotypic switching of adipose tissue macrophages from M1 (proinflammatory) to M2 (anti-inflammatory) type.[54] Moreover, irisin also exerted its anti-inflammatory effects via inhibiting nucleotide-binding domain and NLRP3 (leucine-rich repeat containing family pyrin domain containing 3) inflammasome.[55–58]

Irisin and Oxidative Stress

Irisin could mitigate the severity of the oxygen respiratory burst generated by macrophages[59] and ameliorate reactive oxygen species (ROS)-induced endothelial dysfunction in obese mice.[60] Irisin also could reduce inducible NO synthase and NADPH (nicotinamide adenine dinucleotide phosphate) oxidase level and elevate SOD (superoxide dismutase), GPX-1 (glutathione peroxidase 1), Cat (catalase), Nrf2, and HO-1 in lipopolysaccharide-stimulated murine macrophages[61] and in an ischemia-reperfusion model.[62] In addition, irisin could decrease some metabolic factors, such as high fat– or high glucose–induced oxidative stress in human umbilical vein endothelial cells through inhibiting the activation of PKC-β (protein kinase C-β)/NADPH oxidase pathways.[13]

Irisin and Insulin Resistance

Irisin could regulate the function of pancreatic islets. Irisin was demonstrated to stimulate insulin biosynthesis and accelerate glucose-stimulated insulin secretion in a PKA (protein kinase A)-dependent manner in pancreatic β cells.[14] Under a high-glucose or high-fat environment, irisin could augment the β-cell area and reduce the α-cell area within pancreatic islets,[63] decrease apoptosis of β-cell and stimulate β-cell proliferation, and improve insulin biosynthesis and secretion.[15] In addition, irisin could modulate insulin signaling. For example, irisin overexpression enhanced glucose uptake, glycogen accumulation, and phosphorylation of AMPKα/insulin receptor β-subunit/ERK1/2 in response to insulin treatment in mouse C2C12 myoblasts.[64] A recent study also showed that irisin attenuated palmitic acid-induced inhibition of insulin signaling in rat cardiomyocytes. They found that irisin increased insulin-stimulated glucose consumption through activation of the phosphatidylinositol-3-kinase-Akt (protein kinase B) pathway.[65]

EPIDEMIOLOGICAL STUDIES ON IRISIN IN CVDS

Studies have shown the alteration of circulating irisin concentration in different disease conditions in humans (Table). The results of Lin and colleagues demonstrated that the levels of circulating irisin were positively associated with flow-mediated dilation levels in newly diagnosed Chinese patients with type 2 diabetes mellitus without clinical angiopathy.[66] Similarly, the serum irisin concentrations of patients with diabetes mellitus with atherosclerosis are lower than that of patients with diabetes mellitus without atherosclerosis, indicating that circulating irisin has the potential to act as a diagnostic biomarker for monitoring the progression of CVD in patients with diabetes mellitus.[67,68] Several studies also discovered that serum irisin levels were lower in patients with stable coronary artery disease than healthy controls.[69–71] In addition, it has been shown that different level of severity of coronary artery disease corresponded to different serum irisin levels in patients with stable angina, suggesting that serum irisin can be used to predict the severity of coronary artery disease.[70] Notably, the irisin concentrations in patients with chronic CVD are stable,[72] whereas the irisin concentrations decrease gradually in serum within 48 hours after acute myocardial infarction (MI), suggesting that serum irisin concentration may have an important clinical value used as a diagnostic indicator for the development of acute MI.[73] Furthermore, a clinical study aimed to assess serum irisin level in myocardial infarction MI with or without heart failure, and found that patients with MI and heart failure had reduced serum irisin levels. The authors proposed that serum irisin level could serve as a marker for MI with accuracy similar to creatine kinase-myocardial band, and it is not inferior to creatine kinase-myocardial band in predicting MI.[74]

Irisin levels may also influence the development of hypertension, but the epidemiological data are somewhat complex. A study recruited 98 patients

with hypertension and 24 normotensive controls and found that increased irisin levels were associated with hypertension.[75] Another study also showed that irisin levels were significantly correlated with systolic and diastolic blood pressure in overweight children.[76] However, there are some inconsistent reports. For example, Zhang et al found that the serum levels of irisin were negatively associated with systolic and diastolic blood pressure in patients with preeclampsia.[77] A cross-sectional study including 532 patients with chronic kidney disease provided evidence in favor of the opposite effect of irisin on diastolic blood pressure.[78] Because there is a study reporting a negative correlation between irisin levels and the levels of inflammatory factors,[42] we inferred that irisin reduction in those secondary patients with hypertension might be a response to high levels of inflammation in those individuals. In addition, irisin levels in adults depend on age, sex, obesity, and particularly muscle mass.[79] The different findings across studies may be explained by differences in study populations. Patient selection and differences in dietary components, compliance, and study duration may be critical in determining the different findings.

CARDIOVASCULAR PROTECTION BY IRISIN: EVIDENCE FROM IN VITRO AND ANIMAL STUDIES

Effects of Irisin on Hypertension

Regulation of Central Nervous System

Paraventricular nuclei neurons stimulate the sympathetic preganglionic neurons, participate in the regulation of peripheral sympathetic nerve activity, and are closely related to the occurrence and development of hypertension.[80] A study demonstrated that intravenous injection of irisin once every 2 days for 2 weeks reduced blood pressure, plasma norepinephrine, and paraventricular nuclei neuronal activation in spontaneous hypertensive rates; knockdown of nuclear factor Nrf2 in paraventricular nuclei abolished the protective effects of irisin on hypertension.[81] These indicate that irisin may reduce blood pressure by downregulation of paraventricular nuclei activity (Figure 2).

Vasorelaxation and Improvement of Vascular Dysfunction

Irisin could relax mouse mesenteric arteries through endothelium-dependent and endothelium-independent mechanisms.[34,82,83] Mechanically, endothelium-dependent relaxation of irisin was mediated by the NO-cGMP–dependent pathway and was related to the stimulation of extracellular Ca^{2+} influx via TRPV4 (transient receptor potential vanilloid 4) channels in Sprague-Dawley rats.[83] Endothelium-independent relaxation of irisin may be depended on inhibiting Ca^{2+} influx and on activating ATP-sensitive potassium channels.[34] A study also demonstrated that irisin could facilitate endothelium-dependent vasorelaxation in diabetic aortic segments through increasing NO availability functionally and biochemically.[13] Similarly, Han et al found that chronical irisin treatment improved endothelium-dependent vasodilatation in obese mice through AMPK-endothelial NO synthase pathway.[60] Our previous study also showed that acute administration of irisin lowered the blood pressure of spontaneous hypertensive rates by ameliorating endothelial dysfunction of the mesenteric artery through the AMPK-Akt-NO signaling pathway.[84] On the other hand, irisin also regulated the vascular functions via improving the function of perivascular adipose tissue, an endocrine organ that releases a panel of adipokines and cytokines that participate in the modulation of vascular tone.[85] Hou et al demonstrated that irisin improved the dysfunction of perivascular adipose tissue via regulation of the HO-1/adiponectin axis in diet-induced obese mice.[86]

Improving Insulin Resistance

Both *irisin*-lacking mice and *Fndc5* mutant mice have increased insulin resistance,[46,87] which is an important mechanism causing hypertension. We have also summarized the mechanisms that irisin alleviates insulin resistance by improving pancreatic islet function and insulin signaling in the fourth aspect of the section that entitled as “Irisin and Cardiovascular Risk Factors”. Therefore, irisin may reduce the development of hypertension by improving insulin resistance.

Irisin and Coronary Artery Disease

Irisin and Atherosclerosis

Dysfunction of vascular endothelial cells is a vital pathogenic basis of atherosclerosis, in which the increased oxidative stress and apoptosis of endothelial cells are the main underling mechanisms. Oxidized low-density lipoprotein caused endothelium cell apoptosis, which could be effectively attenuated after pretreatment with irisin.[51,52,88] A study showed that irisin improved endothelial function in diabetic mice,[13] promoted human umbilical vein endothelial cell proliferation and inhibited endothelial cell oxidative stress and apoptosis induced by high glucose[89] or advanced glycation end products.[57] In addition, chronical exogenous treatment with irisin also ameliorated endothelial dysfunction from obesity mice.[90] Moreover, irisin also increased the number and improved the function of endothelial progenitor cells in diabetic mice, indicating that irisin may improve endothelial repair in diabetic mice that

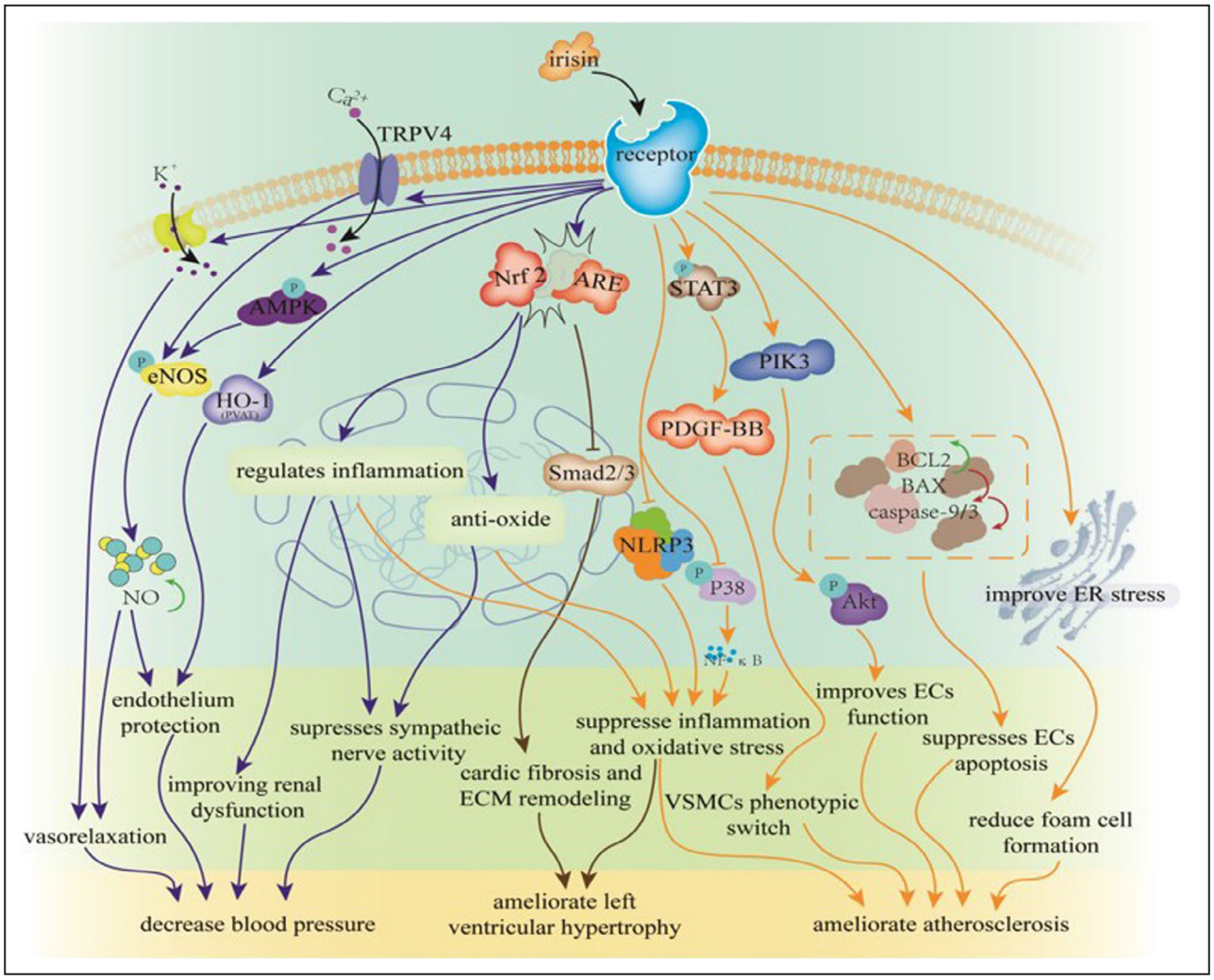

Figure 2. Molecular mechanisms for the protection effects of irisin on decreasing blood pressure, ameliorating left ventricular hypertrophy, and atherosclerosis.

AMPK indicates adenosine monophosphate-activated protein kinase; ARE, antioxidant response element; BAX, BCL2-associated X; BCL2, B-cell lymphoma-2; EC, endothelium cell; ECM, extracellular matrix; eNOS, endothelial NO synthase; ER, endoplasmic reticulum; HO-1, heme oxygenase 1; NLRP3, nucleotide-binding domain and leucine-rich repeat containing family pyrin domain containing 3; Nrf2, nuclear factor E2-related factor 2; PDGF, platelet derived growth factor; PI3K, phosphatidylinositol 3 kinase; PVAT, perivascular adipose tissue; STAT3, signal transducer and activator of transcription; TRPV4, transient receptor potential vanilloid 4; and VSMCs, vascular smooth muscle cells.

received endothelial progenitor cell transplants after carotid artery injury.[91]

Another mechanism by which irisin affects the development of atherosclerosis is via the regulation of inflammation. In vitro studies found that irisin reduced the formation of foam cells induced by oxidized low-density lipoprotein.[92] An in vivo study by Lu et al using the apolipoprotein E–deficient hyperlipidemic and carotid partial ligation mouse model reported the antiatherosclerotic potential of irisin partly through improving inflammation.[51] The authors observed that irisin inhibited the recruitment of inflammatory cells like T lymphocytes and macrophages, leading to reduce the formation of aortic atherosclerotic lesion. The expression of inflammatory mediators such as VCAM-1, ICAM-1, MCP-1, IL-6, and NF-κB were reduced after irisin treatment, which was possibly mediated by suppression of the ROS–p38MAPK–NF-κB pathway.[53] Irisin also alleviated advanced glycation end products–induced inflammation and protected endothelium cells through inhibiting the activation of NLRP3 inflammasome signaling.[57] Moreover, irisin also indirectly regulated the vascular inflammation. For example, irisin inhibited atherosclerosis via upregulation of microRNA126-5p,[93] which has been shown to suppress inflammation in endothelial cells under hyperglycemic conditions.[94]

Vascular smooth muscle cells phenotype modulation is one of the main mechanisms responsible for

atherosclerotic plaque formation.[95] An in vitro study found that irisin inhibited PDGF (platelet derived growth factor)-induced vascular smooth muscle cells phenotype dedifferentiation into synthetic phenotype and proliferative phenotype.[96] Therefore, irisin may exert its antiatherosclerosis effects via modulating the vascular smooth muscle cells phenotype but needed to be further verified (Figure 2).

Irisin and Myocardial Infarction/ Myocardial Ischemia–Reperfusion Injury

Myocardium secretes irisin and contributes to circulating irisin levels.[23] Therefore, it was initially thought that MI might directly increase irisin secretion through damaged cardiomyocytes. However, consistent with those findings in patients, it has been reported that an isoproterenol-induced MI rat model showed the negative relationship between irisin and troponin and creatine phosphokinase-myocardial band isoenzyme, 2 established markers of cardiac damage.[97] These findings imply that irisin is not passively released as a result of cardiomyocyte injury, as does troponin, but is rather energetically secreted, which reflects the sufficiency of blood supply.

Mitochondria serves as the major site for ROS production following myocardial ischemia–reperfusion (MI/R) injury.[98] Studies have shown that irisin protected against MI/R and hypoxia/reoxygenation injury, in association with improved mitochondrial function. For instance, Wang et al found that irisin protected against MI/R through increasing SOD1 expression and p38 phosphorylation, inhibiting the mitochondrial permeability transition pore opening to alleviate mitochondrial dysfunction.[99] Irisin also interacted with SOD2, and restored the mitochondrial localization of SOD2 to ameliorate oxidative stress in response to MI/R injury.[100] A major finding from a recent study revealed that irisin pretreatment protected the heart against MI/R injury, mitochondrial damage, and ROS generation through MITOL (mitochondrial ubiquitin ligase) activation.[101] Moreover, irisin also activated dynamin-like GTPase optic atrophy 1-induced mitophagy, a mechanism to remove damaged mitochondria by autophagy to maintain mitochondrial structure and function,[102] and protected against cardiomyocyte injury following MI.[103]

In addition to the effect on mitochondria, irisin also exerts its effects of anti-MI/R injury via regulating cardiomyocyte apoptosis. Treatment with irisin markedly suppressed the expression of active caspase-3 in cultured cardiomyocytes exposing to hypoxia and subsequent reoxygenation.[104] Furthermore, overexpression of HDAC4 (histone deacetylase 4) has been shown to promote cell death. Irisin reduced HDAC4-induced apoptosis of cardiomyocytes through promoting HDAC4 degradation.[105] Similarly, a study used a Langendorff perfused rat model and showed the protective effect of irisin on MI/R injury, which was ascribed to the increased p38 phosphorylation, consequently resulting in the suppression of cardiomyocytes apoptosis.[99] In addition, a recent study by Zhao et al delineated the potential therapeutic benefit of irisin in cardiac progenitor cell–transplantation for MI because of preconditioning cardiac progenitor cells with irisin-enhanced cardiac repair, improved cardiac function, and reduced cardiac fibrosis.[106]

Angiogenesis is critical for reestablishing blood supply to the ischemic myocardium after MI. An in vitro study found that irisin promoted human umbilical vein endothelial cells proliferation and angiogenesis through the ERK signaling pathway,[89,107] and attenuated oxidized low-density lipoprotein–induced impairment on angiogenesis by activating the Akt/mTOR (mammalian target of the rapamycin)/Nrf2 pathway in endothelium cells.[88] Similarly, Liao et al found that irisin improved cardiac function and reduced infarct size in the post-MI mouse heart, which was associated with its proangiogenic function through activating ERK signaling.[108] In addition, studies have also shown that irisin increased the angiogenesis of transplanted bone marrow mesenchymal stem cells and improved its therapeutic efficacy for MI[109] (Figure 3).

Association of Irisin With Cardiac Hypertrophy and Diabetic Cardiomyopathy

Angiotensin II (Ang-II) contributes to cardiac hypertrophy in response to pressure overload.[110,111] Matsuo and colleagues infused mice with Ang-II for 4 weeks and found that Ang-II reduced FNDC5 protein expression by 45%.[42] In Ang-II–treated cardiomyocytes, irisin expression was also reduced.[112] Moreover, *Fndc5* deficiency aggravated cardiac hypertrophy, but *Fndc5* overexpression attenuated cardiac hypertrophy.[113] Further studies showed the protective effects of irisin on Ang-II–induced cardiomyocyte damage. Irisin induced protective autophagy and reduced cardiomyocyte hypertrophy after Ang-II–induced injury,[112] attenuated Ang-II–mediated cardiac fibrosis via Nrf2 mediated inhibition of ROS/TGF-β1 (transforming growth factor β1) signaling axis,[114] and ameliorated cardiac hypertrophy and fibrosis in a pressure overload murine model[56,115] (Figure 2).

Irisin also has protective effects on diabetic cardiomyopathy. Deng et al found that irisin suppressed the inflammatory responses and oxidative stress in high glucose-injured cardiomyocytes via the AMPK/mTOR signaling pathway.[41] However, another study reported that irisin exerts a dose-dependent bidirectional effect on diabetic cardiomyopathy.[116] The investigators found that at low dosage (0.5 μg/g body

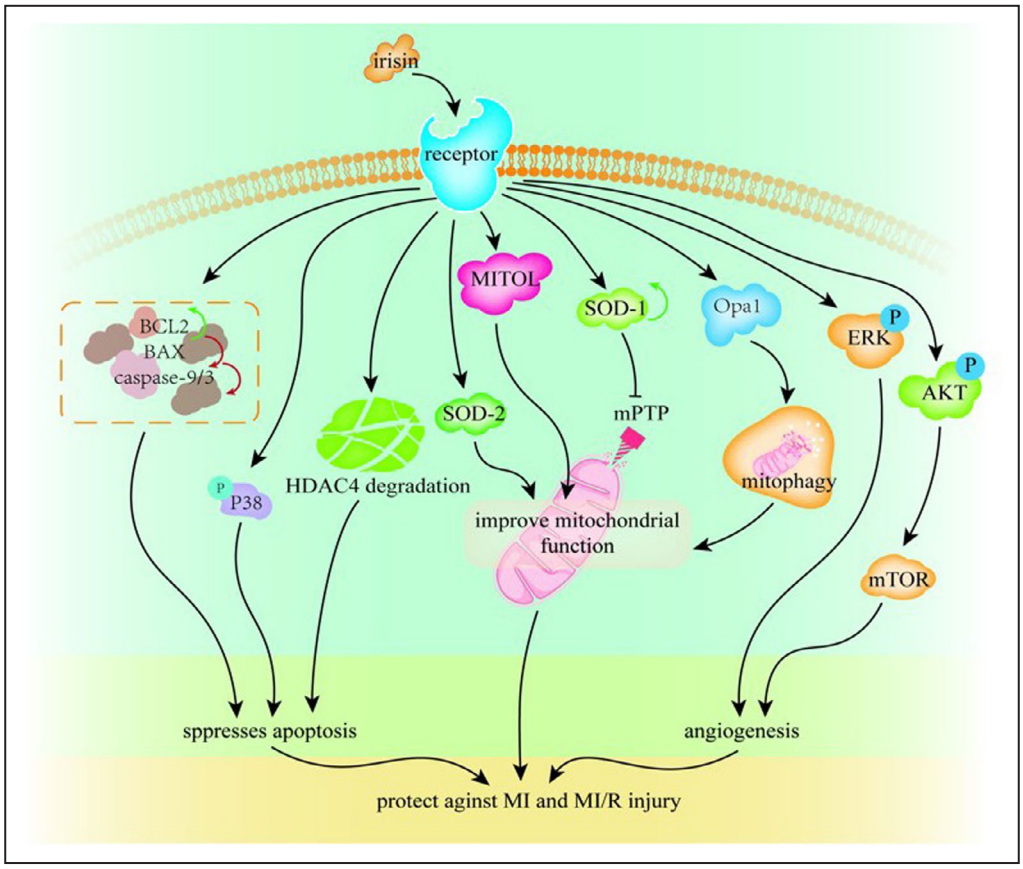

Figure 3. Molecular mechanisms for the protection effects of irisin on myocardial infarction/myocardial ischemia–reperfusion injury.
AKT indicates protein kinase B; BCL-2, B-cell lymphoma-2; BAX, BCL2-associated X; ERK, extracellular regulated protein kinases; HDAC4, histone deacetylases 4; MI, myocardial infarction; MI/R, myocardial ischemia–reperfusion; MITOL, mitochondrial ubiquitin ligase; mPTP, mitochondrial permeability transition pore; mTOR, mammalian target of the rapamycin; Opa1, optic atrophy 1; and SOD, superoxide dismutase.

weight per day), irisin treatment attenuated cardiac fibrosis and protected left ventricular function in diabetic mice via inhibition of high glucose-induced endothelial-to-mesenchymal transition. In contrast, high-dose irisin (1.5 μg/g body weight per day) induced cardiac fibroblast proliferation and migration, which resulted in excess collagen deposition. The mechanism underlying the different effects involved that high dosage irisin enhanced high glucose-induced matrix metalloproteinase expression by inducing MAPK signaling.

Irisin and Other Cardiovascular Diseases

Irisin has also been reported to have beneficial effects on other cardiovascular diseases. Zhang et al recently found that treatment with the chemotherapy drug doxorubicin decreased myocardial level of FNDC5; cardiac-specific overexpression of irisin supplementation alleviates oxidative stress and cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity in mice. Consistent with the data in vivo, irisin treatment exerted similar protective effects on doxorubicin-induced oxidative damage and cardiomyocyte apoptosis in H9C2 cells.[117] These suggest that FNDC5/irisin may be a potential therapeutic agent against doxorubicin-induced cardiotoxicity. In addition, Tang et al reported that irisin treatment ameliorated sepsis-mediated myocardial depression and cardiomyocyte death by inhibiting DRP1 (dynamin-related protein)-related mitochondrial fission.[118]

IRISIN-TARGETED STRATEGIES TO COMBAT CVDS

Irisin and Lifestyle Modifications

Regular exercise is an important nonmedicine treatment to reduce CVDs. The American College of Sports Medicine suggests performing endurance training, flexibility and neuromotor exercise, and regular resistance exercise to improve physical fitness and health.[119] However, irisin has been

Table. Alteration of Circulating Irisin Concentration in Different Disease Conditions in Humans

Disease condition	Method to diagnose disease	Conclusion	Method to detect irisin	Reference
T2DM patients without clinical angiopathy	Patients with clinical angiopathy including micro and macro angiopathy as well as hypertension were excluded from this study.	Higher serum irisin levels were associated with higher FMD levels.	ELISA kits (Aviscera Biosciences)	[66]
T2DM female patients with and without atherosclerosis	Patients were treated by oral hypoglycemic agents and/or insulin.	Decreased serum irisin (32.91±2.545 pg/mL) vs T2DM without atherosclerosis (58.55±13.19 pg/mL).	ELISA kits (Glory Science, cat. no. 95512)	[67]
T2DM patients with CAD	Angiographic evidence of stenosis ≥50% in at least 1 major coronary artery.	Decreased serum irisin (5.4±5.0 ng/mL) vs T2DM without CAD (8.0±6.6 ng/mL).	ELISA kits (Crystal Day Biotechnology)	[68]
Stable patients with CAD	Angiographic evidence of stenosis ≥65% in at least 1 major coronary artery.	Decreased serum irisin (161.24±52.43 ng/mL vs control (217.25±82.55 ng/mL).	ELISA kits (Phoenix Pharmaceuticals)	[69]
Patients with MI	Angiographic evidence of stenosis ≥65% in at least 1 major coronary artery; STEMI and non-STEMI.	Decreased serum irisin (143.54±47.58 ng/mL) vs control (217.25±82.55 ng/mL).	ELISA kits (Phoenix Pharmaceuticals)	[69]
Patients with CAD	Subjects who had angiographic evidence of stenosis ≥50% in at least 1 major coronary artery were considered as patients with CAD. The severity of CAD was assessed by coronary atherosclerosis index.	Higher serum irisin was associated with less burden of coronary atherosclerosis.	ELISA kits (Phoenix Pharmaceuticals)	[70]
Adults at higher cardiovascular risk	Aged 55 y and older with either diabetes mellitus or 2 other cardiovascular risk factors.	Irisin was negatively associated with HDL and was positively associated with large VLDL particles.	ELISA kits (Aviscera Biosciences)	[72]
Patients with acute MI	Requires the following characteristics to be satisfied: (1) typical symptoms, (2) characteristic rise-and-fall pattern of a cardiac marker, and/or (3) a typical ECG pattern involving the development of Q waves.	Saliva and serum irisin concentrations in the acute MI group significantly decreased from 12 h up to 48 h compared with the control group.	ELISA kits (Phoenix Pharmaceuticals, EK-067-16)	73
Patients with MI with and without HF	Myocardial infarction diagnosis requires the following characteristics to be satisfied: (1) typical symptoms, (2) characteristic rise-and-fall pattern of a cardiac marker, and/or (3) a typical ECG pattern involving the development of Q waves. Patients with EF ≤40% (confirmed by echocardiography) were included in HF group.	Decreased serum irisin in MI patients (48.69±2.50 ng/mL) and HF patients (54.31±3.11 ng/mL) compared with control (73.12±5.55 ng/mL).	ELISA kits (Sino Gene Cion Biotech)	[74]
Patients with hypertension	SBP ≥140 mm Hg and/or DBP ≥90 mm Hg were diagnosed with hypertension.	Increased irisin levels were associated with hypertension and hypertension-related stroke.	An adipokine- and myokine-specific Luminex bead-based multiplex detection system (Merck Millipore)	[75]
Overweight or obese children	Nutritional status established for BMI for age, expressed by *z*-score: overweight: >*z*-score +1 and <*z*-score +2 or obesity: >*z*-score +2 and <*z*-score +3.	Increased serum irisin (143.1 vs control 75.2 ng/mL); irisin was positively correlated with metabolic profile and blood pressure.	ELISA kits (Cusabio Life Science, CSB-EQ02793HU)	[76]
Patients with preeclampsia	SBP ≥140 mm Hg or DBP ≥90 mm Hg after 20 wks of gestation in a woman whose blood pressure was previously normal. Proteinuria, with excretion of 0.3 g or more in a 24-h period.	Circulating irisin was negatively correlated with blood pressure.	ELISA kits (Phoenix Pharmaceuticals)	[77]
Patients with CKD	CKD stages 1–5 according to the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative guidelines.	Serum irisin levels were positively correlated with DBP, eGFR, IR, and LDL cholesterol.	ELISA kits (Phoenix Pharmaceuticals)	[78]

BMI indicates body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; EF, ejection fraction; FMD, flow-mediated dilation; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; IR, insulin resistance; LDL, low-density lipoprotein; MI, myocardial infarction; non-STEMI, non–ST-segment–elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST-segment–elevation myocardial infarction; T2DM, type 2 diabetes mellitus; and VLDL, very-low-density lipoprotein.

reported to be augmented in subjects following high-intensity exercise and after resistance training, but not after endurance exercise.[33,120] Therefore, it may be more beneficial through resistance training. Lifestyle interventions are not limited to physical activity but may include dietary supplementations such as omega-3 fatty acids and other natural substances, which have anti-inflammatory properties and protective cardiovascular effects. A cohort study enrolled 45 men with cardiovascular disease and found that the supplementation of omega-3 for 8 weeks caused a significant increase in irisin serum levels with a consequent reduction of high-sensitivity C-reactive protein inflammatory, a predictor of CVDs.[121]

Drugging Strategy for Irisin in Treatment of CVDs

Modulating the serum levels of irisin may be a potential strategy for the treatment of CVDs. Studies have shown that some drugs directly upregulate the FNDC5 expression or the serum levels of irisin. For instance, a clinical study recruited 85 newly diagnosed patients with untreated essential hypertension and found that both amlodipine and valsartan increased the plasma levels of irisin after 12 weeks of treatment.[122] In addition, simvastatin, a lipid-lowering agent, was also found to elevate FNDC5 expression and irisin secretion in humans.[123] However, further studies are still needed to confirm that the effect is mediated by the drug-induced upregulation of irisin, and not the drugs themselves, because the drugs have various cellular effects. Furthermore, the drugging strategy may also include the development of molecules that increase irisin cleavage from the FNDC5 protein or the use of a receptor agonist, although it is still unknown which specific receptor binds to irisin.

CONCLUSIONS AND PERSPECTIVES

Increasing evidence have shown the crucial role of irisin in suppressing risk factors of CVDs and highlighted its emerging role in the prevention and treatment of CVDs (Figures 2 and 3). However, there are some discrepancies in current reports, and the completed mechanisms of irisin in protecting cardiovascular health under pathological conditions have not been fully clarified. The unsolved scientific problem with irisin needs to be studied in the future.

It is important to determine if a specific receptor for irisin on the cell surface of cardiomyocyte exists and to characterize its mode of action. In some tissues, such as vascular endothelial cells,[124] osteocytes,[125] adipocytes,[126] and intestines,[127] irisin exerts its functions via integrins, which are well-known widely expressed transmembrane receptors. In heart tissue, a binding study supported the existence of receptor on the cell surface of cardiomyoblast.[128] Interestingly, irisin was also reported to exert its functions without receptor activation. For example, Chen et al found that irisin, via lipid raft-mediated endocytosis, enters alveolar cells and protects mitochondria function during pulmonary ischemia–reperfusion injury.[129] Therefore, it is worth noting that although the integrin complex has been shown to encapsulate the irisin receptors, this finding does not rule out the presence of irisin receptors of cardiovascular tissue within or outside the integrin family. Further research to find out which receptor binds to irisin on the cell surface of cardiovascular tissue is warranted.

The half-life of irisin is still poorly investigated. A study used irisin radiolabeled with ^{125}I and small-animal single photon emission computed tomography/computed tomography imaging to investigate the metabolic elimination and distribution of irisin in vivo, showing that metabolic clearance of ^{125}I-irisin was achieved primarily through the hepatobiliary and renal system.[130] The 2 systems act together to determine the metabolic clearance rate of irisin in vivo. The authors found that radioactivity of the gallbladder, followed by the liver and kidneys, decreased gradually from 30 to 120 minutes, and reduced to its concentration almost by half at 60 minutes. However, they did not point out the exact half-life of irisin, which also needs further investigation.

Studies have shown that irisin could directly relax mouse mesenteric arteries.[82,83] However, our previous study found that irisin could not induce direct dilation in small resistant vessels but only ameliorate endothelial dysfunction of the mesenteric artery from spontaneous hypertensive rates.[84] The reasons leading to the difference are not known. Thus, more well-designed studies to investigate the direct vasorelaxant effects of irisin in various vascular beds, including macro and micro vasculatures from various experimental animal models, are needed.

In addition, the kidney is the major organ involved in sodium homeostasis and plays a vital role in the long-term control of blood pressure. Studies have indicated an association between circulating levels of irisin and renal functions.[131] However, it is still unknown about the regulation of irisin in renal sodium homeostasis, which also opens a window for scholars to conduct in-depth studies.

Further study to complete the description of the underling mechanisms involved in irisin synthesis and secretion by muscle tissue during exercise is also needed. Such information might help to explain the differences between acute and chronic training on circulating levels of irisin and reveal additional stimulators for irisin secretion.

Epidemiological studies have shown that irisin single-nucleotide polymorphisms, rs3480 and rs726344, increased the risk of developing MI.[132] However, whether *irisin* gene variants are also associated with other CVDs, such as atherosclerosis and hypertension, are still mysteries that also need to be elucidated.

In conclusion, with continued progress in understanding the role and mechanisms of irisin in the CVDs, we believe that its use in the treatment of CVDs will be hopeful.

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REFERENCES

1. Sattar N, Gill JMR, Alazawi W. Improving prevention strategies forcardiometabolic disease. *Nat Med*. 2020;26:320–325. DOI: 10.1038/s41591-020-0786-7.
2. Ma LY, Chen WW, Gao RL, Liu LS, Zhu ML, Wang YJ, Wu ZS, Li HJ, Gu DF, Yang YJ, et al. China cardiovascular diseases report 2018: an updated summary. *J Geriatr Cardiol*. 2020;17:1–8. DOI: 10.11909/j.issn.1671-5411.2020.01.001.
3. Streese L, Guerini C, Buhlmayer L, Lona G, Hauser C, Bade S, Deiseroth A, Hanssen H. Physical activity and exercise improve retinal microvascular health as a biomarker of cardiovascular risk: a systematic review. *Atherosclerosis*. 2020;315:33–42. DOI: 10.1016/j.atherosclerosis.2020.09.017.
4. Frodermann V, Rohde D, Courties G, Severe N, Schloss MJ, Amatullah H, McAlpine CS, Cremer S, Hoyer FF, Ji F, et al. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nat Med*. 2019;25:1761–1771. DOI: 10.1038/s41591-019-0633-x.
5. Bernardo BC, Ooi JYY, Weeks KL, Patterson NL, McMullen JR. Understanding key mechanisms of exercise-induced cardiac protection to mitigate disease: current knowledge and emerging concepts. *Physiol Rev*. 2018;98:419–475. DOI: 10.1152/physrev.00043.2016.
6. Severinsen MCK, Pedersen BK. Muscle–organ crosstalk: the emerging roles of myokines. *Endocr Rev*. 2020;41:594–609. DOI: 10.1210/endrev/bnaa016.
7. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol*. 2012;8:457–465. DOI: 10.1038/nrendo.2012.49.
8. Cho J, Choi Y, Sajgalik P, No MH, Lee SH, Kim S, Heo JW, Cho EJ, Chang E, Kang JH, et al. Exercise as a therapeutic strategy for sarcopenia in heart failure: insights into underlying mechanisms. *Cells*. 2020;9:2284. DOI: 10.3390/cells9102284.
9. Gomez-Samano MA, Grajales-Gomez M, Zuarth-Vazquez JM, Navarro-Flores MF, Martinez-Saavedra M, Juarez-Leon OA, Morales-Garcia MG, Enriquez-Estrada VM, Gomez-Perez FJ, Cuevas-Ramos D. Fibroblast growth factor 21 and its novel association with oxidative stress. *Redox Biol*. 2017;11:335–341. DOI: 10.1016/j.redox.2016.12.024.
10. Rothman SM, Griffioen KJ, Wan R, Mattson MP. Brain-derived neurotrophic factor as a regulator of systemic and brain energy metabolism and cardiovascular health. *Ann N Y Acad Sci*. 2012;1264:49–63. DOI: 10.1111/j.1749-6632.2012.06525.x.
11. Castillo-Quan JI. From white to brown fat through the pgc-1alpha-dependent myokine irisin: implications for diabetes and obesity. *Dis Model Mech*. 2012;5:293–295.
12. Mazur-Bialy AI, Pochec E, Zarawski M. Anti-inflammatory properties of irisin, mediator of physical activity, are connected with TLR4/Myd88 signaling pathway activation. *Int J Mol Sci*. 2017;18:701. DOI: 10.3390/ijms18040701.
13. Zhu DI, Wang H, Zhang J, Zhang X, Xin C, Zhang F, Lee Y, Zhang L, Lian K, Yan W, et al. Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses. *J Mol Cell Cardiol*. 2015;87:138–147. DOI: 10.1016/j.yjmcc.2015.07.015.
14. Natalicchio A, Marrano N, Biondi G, Spagnuolo R, Labarbuta R, Porreca I, Cignarelli A, Bugliani M, Marchetti P, Perrini S, et al. The myokine irisin is released in response to saturated fatty acids and promotes pancreatic beta-cell survival and insulin secretion. *Diabetes*. 2017;66:2849–2856. DOI: 10.2337/db17-0002.
15. Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE, Tsoukas MA, Geladari EV, Huh JY, Dincer F, et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. *J Clin Endocrinol Metab*. 2013;98:4899–4907. DOI: 10.1210/jc.2013-2373.
16. Mo L, Shen J, Liu Q, Zhang Y, Kuang J, Pu S, Cheng S, Zou M, Jiang W, Jiang C, et al. Irisin is regulated by car in liver and is a mediator of hepatic glucose and lipid metabolism. *Mol Endocrinol*. 2016;30:533–542. DOI: 10.1210/me.2015-1292.
17. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Bostrom EA, Choi JH, Long JZ, et al. A pgc1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481:463–468. DOI: 10.1038/nature10777.
18. Metwally M, Bayoumi A, Romero-Gomez M, Thabet K, John M, Adams LA, Huo X, Aller R, García-Monzón C, Teresa Arias-Loste M, et al. A polymorphism in the irisin-encoding gene (FNDC5) associates with hepatic steatosis by differential miRNA binding to the 3'UTR. *J Hepatol*. 2019;70:494–500. DOI: 10.1016/j.jhep.2018.10.021.
19. Medicine KDP. Irisin, light my fire. *Science*. 2012;336:42–43. DOI: 10.1126/science.1221688.
20. Schumacher MA, Chinnam N, Ohashi T, Shah RS, Erickson HP. The structure of irisin reveals a novel intersubunit beta-sheet fibronectin type III (FNIII) dimer: implications for receptor activation. *J Biol Chem*. 2013;288:33738–33744. DOI: 10.1074/jbc.M113.516641.
21. Yu Q, Kou W, Xu XU, Zhou S, Luan P, Xu X, Li H, Zhuang J, Wang J, Zhao Y, et al. FNDC5/Irisin inhibits pathological cardiac hypertrophy. *Clin Sci*. 2019;133:611–627. DOI: 10.1042/CS20190016.
22. Roca-Rivada A, Castelao C, Senin LL, Landrove MO, Baltar J, Belen Crujeiras A, Seoane LM, Casanueva FF, Pardo M. FNDC5/Irisin is not only a myokine but also an adipokine. *PLoS One*. 2013;8:e60563. DOI: 10.1371/journal.pone.0060563.
23. Aydin S, Kuloglu T, Aydin S, Eren MN, Celik A, Yilmaz M, Kalayci M, Sahin İ, Gungor O, Gurel A, et al. Cardiac, skeletal muscle and serum irisin responses to with or without water exercise in young and old male rats: cardiac muscle produces more irisin than skeletal muscle. *Peptides*. 2014;52:68–73. DOI: 10.1016/j.peptides.2013.11.024.
24. Martin AR, Chung S, Koehler K. Is exercise a match for cold exposure? Common molecular framework for adipose tissue browning. *Int J Sports Med*. 2020;41:427–442. DOI: 10.1055/a-1100-7118.
25. Polyzos SA, Mantzoros CS. An update on the validity of irisin assays and the link between irisin and hepatic metabolism. *Metabolism*. 2015;64:937–942. DOI: 10.1016/j.metabol.2015.06.005.

26. Sanchis-Gomar F, Alis R, Pareja-Galeano H, Romagnoli M, Perez-Quilis C. Inconsistency in circulating irisin levels: what is really happening? *Horm Metab Res*. 2014;46:591–596. DOI: 10.1055/s-0033-1363283.
27. Bostrom PA, Fernandez-Real JM, Mantzoros C. Irisin in humans: recent advances and questions for future research. *Metabolism*. 2014;63:178–180. DOI: 10.1016/j.metabol.2013.11.009.
28. Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS, Gygi SP, Spiegelman BM. Detection and quantitation of circulating human irisin by tandem mass spectrometry. *Cell Metab*. 2015;22:734–740. DOI: 10.1016/j.cmet.2015.08.001.
29. Tsuchiya Y, Ando D, Takamatsu K, Goto K. Resistance exercise induces a greater irisin response than endurance exercise. *Metabolism*. 2015;64:1042–1050. DOI: 10.1016/j.metabol.2015.05.010.
30. Young MF, Valaris S, Wrann CD. A role for FNDC5/irisin in the beneficial effects of exercise on the brain and in neurodegenerative diseases. *Prog Cardiovasc Dis*. 2019;62:172–178. DOI: 10.1016/j.pcad.2019.02.007.
31. Li DJ, Li YH, Yuan HB, Qu LF, Wang P. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism*. 2017;68:31–42. DOI: 10.1016/j.metabol.2016.12.003.
32. Huh JY, Mougios V, Skraparlis A, Kabasakalis A, Mantzoros CS. Irisin in response to acute and chronic whole-body vibration exercise in humans. *Metabolism*. 2014;63:918–921. DOI: 10.1016/j.metabol.2014.04.001.
33. Nygaard H, Slettalokken G, Vegge G, Hollan I, Whist JE, Strand T, Ronnestad BR, Ellefsen S. Irisin in blood increases transiently after single sessions of intense endurance exercise and heavy strength training. *PLoS One*. 2015;10:e0121367. DOI: 10.1371/journal.pone.0121367.
34. Zhang W, Chang L, Zhang C, Zhang R, Li Z, Chai B, Li J, Chen E, Mulholland M. Central and peripheral irisin differentially regulate blood pressure. *Cardiovasc Drugs Ther*. 2015;29:121–127. DOI: 10.1007/s10557-015-6580-y.
35. Huh JY, Mougios V, Kabasakalis A, Fatouros I, Siopi A, Douroudos II, Filippaios A, Panagiotou G, Park KH, Mantzoros CS. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through ampk activation. *J Clin Endocrinol Metab*. 2014;99:E2154–E2161. DOI: 10.1210/jc.2014-1437.
36. Qiao X, Nie Y, Ma Y, Chen Y, Cheng R, Yin W, Hu Y, Xu W, Xu L. Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways. *Sci Rep*. 2016;6:18732. DOI: 10.1038/srep18732.
37. Lally JS, Ford RJ, Johar J, Crane JD, Kemp BE, Steinberg GR. Skeletal muscle AMPK is essential for the maintenance of FNDC5 expression. *Physiol Rep*. 2015;3:e12343. DOI: 10.14814/phy2.12343.
38. Huh JY, Dincer F, Mesfum E, Mantzoros CS. Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans. *Int J Obes (Lond)*. 2014;38:1538–1544. DOI: 10.1038/ijo.2014.42.
39. Lee P, Linderman J, Smith S, Brychta R, Wang J, Idelson C, Perron R, Werner C, Phan G, Kammula U, et al. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. *Cell Metab*. 2014;19:302–309. DOI: 10.1016/j.cmet.2013.12.017.
40. Guo Q, Wei X, Hu H, Yang D, Zhang B, Fan X, Liu J, He H, Oh Y, Wu Q, et al. The saturated fatty acid palmitate induces insulin resistance through Smad3-mediated down-regulation of FNDC5 in myotubes. *Biochem Biophys Res Commun*. 2019;520:619–626. DOI: 10.1016/j.bbrc.2019.10.077.
41. Deng J, Zhang N, Chen F, Yang C, Ning H, Xiao C, Sun KE, Liu Y, Yang M, Hu T, et al. Irisin ameliorates high glucose-induced cardiomyocytes injury via AMPK/mTOR signal pathway. *Cell Biol Int*. 2020;44:2315–2325. DOI: 10.1002/cbin.11441.
42. Matsuo Y, Gleitsmann K, Mangner N, Werner S, Fischer T, Bowen TS, Kricke A, Matsumoto Y, Kurabayashi M, Schuler G, et al. Fibronectin type III domain containing 5 expression in skeletal muscle in chronic heart failure-relevance of inflammatory cytokines. *J Cachexia Sarcopenia Muscle*. 2015;6:62–72. DOI: 10.1002/jcsm.12006.
43. Perakakis N, Triantafyllou GA, Fernandez-Real JM, Huh JY, Park KH, Seufert J, Mantzoros CS. Physiology and role of irisin in glucose homeostasis. *Nature reviews. Endocrinol*. 2017;13:324–337. DOI: 10.1038/nrendo.2016.221.
44. So WY, Leung PS. Irisin ameliorates hepatic glucose/lipid metabolism and enhances cell survival in insulin-resistant human HepG2 cells through adenosine monophosphate-activated protein kinase signaling. *Int J Biochem Cell Biol*. 2016;78:237–247. DOI: 10.1016/j.biocel.2016.07.022.
45. Ricquier D. UCP1, the mitochondrial uncoupling protein of brown adipocyte: a personal contribution and a historical perspective. *Biochimie*. 2017;134:3–8. DOI: 10.1016/j.biochi.2016.10.018.
46. Xiong Y, Wu Z, Zhang B, Wang C, Mao F, Liu X, Hu K, Sun X, Jin W, Kuang S. FNDC5 loss-of-function attenuates exercise-induced browning of white adipose tissue in mice. *FASEB J*. 2019;33:5876–5886. DOI: 10.1096/fj.201801754RR.
47. Zhang Y, Xie C, Wang H, Foss RM, Clare M, George EV, Li S, Katz A, Cheng H, Ding Y, et al. Irisin exerts dual effects on browning and adipogenesis of human white adipocytes. *Am J Physiol Endocrinol Metab*. 2016;311:E530–E541. DOI: 10.1152/ajpendo.00094.2016.
48. Zhang Y, Li R, Meng Y, Li S, Donelan W, Zhao Y, Qi L, Zhang M, Wang X, Cui T, et al. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. *Diabetes*. 2014;63:514–525. DOI: 10.2337/db13-1106.
49. Tsai YC, Wang CW, Wen BY, Hsieh PS, Lee YM, Yen MH, Cheng PY. Involvement of the p62/Nrf2/HO-1 pathway in the browning effect of irisin in 3T3-L1 adipocytes. *Mol Cell Endocrinol*. 2020;514:110915. DOI: 10.1016/j.mce.2020.110915.
50. Moreno-Navarrete JM, Ortega F, Serrano M, Guerra E, Pardo G, Tinahones F, Ricart W, Fernandez-Real JM. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. *J Clin Endocrinol Metab*. 2013;98:E769–E778. DOI: 10.1210/jc.2012-2749.
51. 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;243:438–448. DOI: 10.1016/j.atherosclerosis.2015.10.020.
52. Zhang Y, Mu Q, Zhou Z, Song H, Zhang Y, Wu F, Jiang M, Wang F, Zhang W, Li L, et al. Protective effect of irisin on atherosclerosis via suppressing oxidized low density lipoprotein induced vascular inflammation and endothelial dysfunction. *PLoS One*. 2016;11:e0158038. DOI: 10.1371/journal.pone.0158038.
53. Mazur-Bialy AI. Superiority of the non-glycosylated form over the glycosylated form of irisin in the attenuation of adipocytic meta-inflammation: a potential factor in the fight against insulin resistance. *Biomolecules*. 2019;9:394. DOI: 10.3390/biom9090394.
54. Dong J, Dong Y, Dong Y, Chen F, Mitch WE, Zhang L. Inhibition of myostatin in mice improves insulin sensitivity via irisin-mediated cross talk between muscle and adipose tissues. *Int J Obes (Lond)*. 2016;40:434–442. DOI: 10.1038/ijo.2015.200.
55. Li Q, Tan Y, Chen S, Xiao X, Zhang M, Wu Q, Dong M. Irisin alleviates lps-induced liver injury and inflammation through inhibition of NLRP3 inflammasome and NF-kappab signaling. *J Recept Signal Transduct Res*. 2021;41:294–303.
56. Yue R, Zheng Z, Luo Y, Wang X, Lv M, Qin D, Tan Q, Zhang Y, Wang T, Hu H. Nlrp3-mediated pyroptosis aggravates pressure overload-induced cardiac hypertrophy, fibrosis, and dysfunction in mice: cardioprotective role of irisin. *Cell Death Discov*. 2021;7:50. DOI: 10.1038/s41420-021-00434-y.
57. Deng X, Huang W, Peng J, Zhu T-T, Sun X-L, Zhou X-Y, Yang H, Xiong J-F, He H-Q, Xu Y-H, et al. Irisin alleviates advanced glycation end products-induced inflammation and endothelial dysfunction via inhibiting ROS-NLRP3 inflammasome signaling. *Inflammation*. 2018;41:260–275. DOI: 10.1007/s10753-017-0685-3.
58. Peng J, Deng X, Huang W, Yu J-H, Wang J-X, Wang J-P, Yang S-B, Liu XI, Wang LI, Zhang Y, et al. Irisin protects against neuronal injury induced by oxygen-glucose deprivation in part depends on the inhibition of ROS-NLRP3 inflammatory signaling pathway. *Mol Immunol*. 2017;91:185–194. DOI: 10.1016/j.molimm.2017.09.014.
59. Mazur-Bialy AI. Irisin acts as a regulator of macrophages host defense. *Life Sci*. 2017;176:21–25. DOI: 10.1016/j.lfs.2017.03.011.
60. Han F, Zhang S, Hou N, Wang D, Sun X. Irisin improves endothelial function in obese mice through the AMPK-eNOS pathway. *Am J Physiol Heart Circ Physiol*. 2015;309:H1501–H508. DOI: 10.1152/ajpheart.00443.2015.
61. Mazur-Bialy AI, Kozlowska K, Pochec E, Bilski J, Brzozowski T. Myokine irisin induced protection against oxidative stress in vitro. Involvement of heme oxygenase-1 and antioxidazing enzymes superoxide dismutase-2 and glutathione peroxidase. *J Physiol Pharmacol*. 2018;69:117–125. DOI: 10.26402/jpp.2018.1.13.

62. Szabo MR, Pipicz M, Csont T, Csonka C. Modulatory effect of myokines on reactive oxygen species in ischemia/reperfusion. *Int J Mol Sci*. 2020;21:9382. DOI: 10.3390/ijms21249382.
63. Liu S, Du F, Li X, Wang M, Duan R, Zhang J, Wu Y, Zhang Q. Effects and underlying mechanisms of irisin on the proliferation and apoptosis of pancreatic beta cells. *PLoS One*. 2017;12:e0175498. DOI: 10.1371/journal.pone.0175498.
64. Yano N, Zhang L, Wei D, Dubielecka PM, Wei L, Zhuang S, Zhu P, Qin G, Liu PY, Chin YE, et al. Irisin counteracts high glucose and fatty acid-induced cytotoxicity by preserving the AMPK-insulin receptor signaling axis in C2C12 myoblasts. *Am J Physiol Endocrinol Metab*. 2020;318:E791–E805. DOI: 10.1152/ajpendo.00219.2019.
65. Song R, Zhao X, Cao R, Liang Y, Zhang DQ, Wang R. Irisin improves insulin resistance by inhibiting autophagy through the PI3K/Akt pathway in H9c2 cells. *Gene*. 2021;769:145209. DOI: 10.1016/j.gene.2020.145209.
66. Xiang L, Xiang G, Yue L, Zhang J, Zhao L. Circulating irisin levels are positively associated with endothelium-dependent vasodilation in newly diagnosed type 2 diabetic patients without clinical angiopathy. *Atherosclerosis*. 2014;235:328–333. DOI: 10.1016/j.atherosclerosis.2014.04.036.
67. Saadeldin MK, Elshaer SS, Emara IA, Maged M, Abdel-Aziz AK. Serum sclerostin and irisin as predictive markers for atherosclerosis in Egyptian type II diabetic female patients: a case control study. *PLoS One*. 2018;13:e0206761. DOI: 10.1371/journal.pone.0206761.
68. Khorasani ZM, Bagheri RK, Yaghoubi MA, Chobkar S, Aghaee MA, Abbaszadegan MR, Sahebkar A. The association between serum irisin levels and cardiovascular disease in diabetic patients. *Diabetes Metab Syndr*. 2019;13:786–790. DOI: 10.1016/j.dsx.2018.11.050.
69. Anastasilakis AD, Koulaxis D, Kefala N, Polyzos SA, Upadhyay J, Pagkalidou E, Economou F, Anastasilakis CD, Mantzoros CS. Circulating irisin levels are lower in patients with either stable coronary artery disease (CAD) or myocardial infarction (MI) versus healthy controls, whereas follistatin and activin a levels are higher and can discriminate MI from CAD with similar to CK-MB accuracy. *Metabolism*. 2017;73:1–8. DOI: 10.1016/j.metabol.2017.05.002.
70. Deng W. Association of serum irisin concentrations with presence and severity of coronary artery disease. *Med Sci Monit*. 2016;22:4193–4197. DOI: 10.12659/MSM.897376.
71. Guo W, Zhang B, Wang X. Lower irisin levels in coronary artery disease: a meta analysis. *Minerva Endocrinol*. 2020;45:61–69. DOI: 10.23736/S0391-1977.17.02663-3.
72. Panagiotou G, Mu L, Na B, Mukamal KJ, Mantzoros CS. Circulating irisin, omentin-1, and lipoprotein subparticles in adults at higher cardiovascular risk. *Metabolism*. 2014;63:1265–1271. DOI: 10.1016/j.metabol.2014.06.001.
73. Aydin S, Aydin S, Kobat MA, Kalayci M, Eren MN, Yilmaz M, Kuloglu T, Gul E, Secen O, Alatas OD, et al. Decreased saliva/serum irisin concentrations in the acute myocardial infarction promising for being a new candidate biomarker for diagnosis of this pathology. *Peptides*. 2014;56:141–145. DOI: 10.1016/j.peptides.2014.04.002.
74. Abd El-Mottaleb NA, Galal HM, El Maghraby KM, Gadallah AI. Serum irisin level in myocardial infarction patients with or without heart failure. *Can J Physiol Pharmacol*. 2019;97:932–938. DOI: 10.1139/cjpp-2018-0736.
75. Chen K, Zhou M, Wang X, Li S, Yang D. The role of myokines and adipokines in hypertension and hypertension-related complications. *Hypertens Res*. 2019;42:1544–1551. DOI: 10.1038/s41440-019-0266-y.
76. De Meneck F, Victorino de Souza L, Oliveira V, do Franco MC. High irisin levels in overweight/obese children and its positive correlation with metabolic profile, blood pressure, and endothelial progenitor cells. *Nutr Metab Cardiovasc Dis*. 2018;28:756–764. DOI: 10.1016/j.numecd.2018.04.009.
77. Zhang LJ, Xie Q, Tang CS, Zhang AH. Expressions of irisin and urotensin II and their relationships with blood pressure in patients with preeclampsia. *Clin Exp Hypertens*. 2017;39:460–467. DOI: 10.1080/10641963.2016.1273945.
78. Ebert T, Focke D, Petroff D, Wurst U, Richter J, Bachmann A, Lössner U, Kralisch S, Kratzsch J, Beige J, et al. Serum levels of the myokine irisin in relation to metabolic and renal function. *Eur J Endocrinol*. 2014;170:501–506. DOI: 10.1530/EJE-13-1053.
79. Löffler D, Müller U, Scheuermann K, Friebe D, Gesing J, Bielitz J, Erbs S, Landgraf K, Wagner IV, Kiess W, et al. Serum irisin levels are regulated by acute strenuous exercise. *J Clin Endocrinol Metab*. 2015;100:1289–1299. DOI: 10.1210/jc.2014-2932.
80. Chen WW, Xiong XQ, Chen Q, Li YH, Kang YM, Zhu GQ. Cardiac sympathetic afferent reflex and its implications for sympathetic activation in chronic heart failure and hypertension. *Acta Physiol (Oxf)*. 2015;213:778–794. DOI: 10.1111/apha.12447.
81. Huo C-J, Yu X-J, Sun Y-J, Li H-B, Su Q, Bai J, Li Y, Liu K-L, Qi J, Zhou S-W, et al. Irisin lowers blood pressure by activating the nrf2 signaling pathway in the hypothalamic paraventricular nucleus of spontaneously hypertensive rats. *Toxicol Appl Pharmacol*. 2020;394:114953. DOI: 10.1016/j.taap.2020.114953.
82. Jiang M, Wan F, Wang F, Wu Q. Irisin relaxes mouse mesenteric arteries through endothelium-dependent and endothelium-independent mechanisms. *Biochem Biophys Res Commun*. 2015;468:832–836. DOI: 10.1016/j.bbrc.2015.11.040.
83. Ye L, Xu M, Hu M, Zhang H, Tan X, Li Q, Shen B, Huang J. TRPV4 is involved in irisin-induced endothelium-dependent vasodilation. *Biochem Biophys Res Commun*. 2018;495:41–45. DOI: 10.1016/j.bbrc.2017.10.160.
84. Fu J, Han Y, Wang J, Liu Y, Zheng S, Zhou L, Jose PA, Zeng C. Irisin lowers blood pressure by improvement of endothelial dysfunction via AMPK-Akt-eNOS-NO pathway in the spontaneously hypertensive rat. *J Am Heart Assoc*. 2016;5:e003433. DOI: 10.1161/JAHA.116.003433.
85. Zaborska KE, Wareing M, Austin C. Comparisons between perivascular adipose tissue and the endothelium in their modulation of vascular tone. *Br J Pharmacol*. 2017;174:3388–3397. DOI: 10.1111/bph.13648.
86. Hou N, Liu Y, Han F, Wang D, Hou X, Hou S, Sun X. Irisin improves perivascular adipose tissue dysfunction via regulation of the heme oxygenase-1/adiponectin axis in diet-induced obese mice. *J Mol Cell Cardiol*. 2016;99:188–196. DOI: 10.1016/j.yjmcc.2016.09.005.
87. Luo Y, Qiao X, Ma Y, Deng H, Xu CC, Xu L. Disordered metabolism in mice lacking irisin. *Sci Rep*. 2020;10:17368. DOI: 10.1038/s41598-020-74588-7.
88. Zhang M, Xu Y, Jiang L. Irisin attenuates oxidized low-density lipoprotein impaired angiogenesis through akt/mtor/s6k1/nrf2 pathway. *Sci Rep*. 2019;234:18951–18962. DOI: 10.1002/jcp.28535.
89. Song H, Wu F, Zhang Y, Zhang Y, Wang F, Jiang M, Wang Z, Zhang M, Li S, Yang L, 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:e110273. DOI: 10.1371/journal.pone.0110273.
90. Hou N, Du G, Han F, Zhang J, Jiao X, Sun X. Irisin regulates heme oxygenase-1/adiponectin axis in perivascular adipose tissue and improves endothelial dysfunction in diet-induced obese mice. *Cell Physiol Biochem*. 2017;42:603–614. DOI: 10.1159/000477864.
91. Zhu G, Wang J, Song M, Zhou F, Fu D, Ruan G, Zhu X, Bai Y, Huang L, Pang R, et al. Irisin increased the number and improved the function of endothelial progenitor cells in diabetes mellitus mice. *J Cardiovasc Pharmacol*. 2016;68:67–73. DOI: 10.1097/FJC.0000000000000386.
92. Zheng G, Li H, Zhang T, Yang L, Yao S, Chen S, Zheng M, Zhao Q, Tian H. Irisin protects macrophages from oxidized low density lipoprotein-induced apoptosis by inhibiting the endoplasmic reticulum stress pathway. *Saudi J Biol Sci*. 2018;25:849–857. DOI: 10.1016/j.sjbs.2017.08.018.
93. Zhang Y, Song H, Zhang Y, Wu F, Mu Q, Jiang M, Wang F, Zhang W, Li L, Shao L, et al. Irisin inhibits atherosclerosis by promoting endothelial proliferation through microrna126-5p. *J Am Heart Assoc*. 2016;5:e004031. DOI: 10.1161/JAHA.116.004031.
94. Tang ST, Wang F, Shao M, Wang Y, Zhu HQ. Microrna-126 suppresses inflammation in endothelial cells under hyperglycemic condition by targeting HMGB1. *Vascul Pharmacol*. 2017;88:48–55. DOI: 10.1016/j.vph.2016.12.002.
95. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res*. 2016;118:692–702. DOI: 10.1161/CIRCRESAHA.115.306361.
96. Song H, Xu J, Lv N, Zhang Y, Wu F, Li H, Shao L, Mu Q, Wang F, Tang D, et al. Irisin reverses platelet derived growth factor-bb-induced vascular smooth muscle cells phenotype modulation through STAT3 signaling pathway. *Biochem Biophys Res Commun*. 2016;479:139–145. DOI: 10.1016/j.bbrc.2016.07.052.
97. Hassaan PS, Nassar SZ, Issa Y, Zahran N. Irisin vs. Treadmill exercise in post myocardial infarction cardiac rehabilitation in rats. *Arch Med Res*. 2019;50:44–54. DOI: 10.1016/j.arcmed.2019.05.009.
98. Elrod JW, Calvert JW, Morrison J, Doeller JE, Kraus DW, Tao L, Jiao X, Scalia R, Kiss L, Szabo C, et al. Hydrogen sulfide attenuates myocardial

ischemia-reperfusion injury by preservation of mitochondrial function. *Proc Natl Acad Sci*. 2007;104:15560–15565. DOI: 10.1073/pnas.0705891104.
99. Wang H, Zhao YT, Zhang S, Dubielecka PM, Du J, Yano N, Chin YE, Zhuang S, Qin G, Zhao TC. Irisin plays a pivotal role to protect the heart against ischemia and reperfusion injury. *J Cell Physiol*. 2017;232:3775–3785. DOI: 10.1002/jcp.25857.
100. Wang Z, Chen K, Han YU, Zhu H, Zhou X, Tan T, Zeng J, Zhang J, Liu Y, Li YU, et al. Irisin protects heart against ischemia-reperfusion injury through a SOD2-dependent mitochondria mechanism. *J Cardiovasc Pharmacol*. 2018;72:259–269. DOI: 10.1097/FJC.0000000000000608.
101. Lu L, Ma J, Tang J, Liu Y, Zheng Q, Chen S, Gao E, Ren J, Yang L, Yang J. Irisin attenuates myocardial ischemia/reperfusion-induced cardiac dysfunction by regulating ER-mitochondria interaction through a mitochondrial ubiquitin ligase-dependent mechanism. *Clin Transl Med*. 2020;10:e166. DOI: 10.1002/ctm2.166.
102. Zhou H, He L, Xu G, Chen L. Mitophagy in cardiovascular disease. *Clin Chim Acta*. 2020;507:210–218. DOI: 10.1016/j.cca.2020.04.033.
103. Xin T, Lu C. Irisin activates Opa1-induced mitophagy to protect cardiomyocytes against apoptosis following myocardial infarction. *Aging*. 2020;12:4474–4488. DOI: 10.18632/aging.102899.
104. Moscoso I, Cebro-Marquez M, Rodriguez-Manero M, Gonzalez-Juanatey JR, Lage R. FNDC5/Irisin counteracts lipotoxic-induced apoptosis in hypoxic H9c2 cells. *J Mol Endocrinol*. 2019;63:151–159. DOI: 10.1530/JME-19-0123.
105. Zhao YT, Wang H, Zhang S, Du J, Zhuang S, Zhao TC. Irisin ameliorates hypoxia/reoxygenation-induced injury through modulation of histone deacetylase 4. *PLoS One*. 2016;11:e0166182. DOI: 10.1371/journal.pone.0166182.
106. Zhao YT, Wang J, Yano N, Zhang LX, Wang H, Zhang S, Qin G, Dubielecka PM, Zhuang S, Liu PY, et al. Irisin promotes cardiac progenitor cell-induced myocardial repair and functional improvement in infarcted heart. *J Cell Physiol*. 2019;234:1671–1681. DOI: 10.1002/jcp.27037.
107. Wu F, Song H, Zhang Y, Zhang Y, Mu Q, Jiang M, Wang F, Zhang W, Li L, Li H, 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:e0134662. DOI: 10.1371/journal.pone.0134662.
108. Liao Q, Qu S, Tang LX, Li LP, He DF, Zeng CY, Wang WE. Irisin exerts a therapeutic effect against myocardial infarction via promoting angiogenesis. *Acta Pharmacol Sin*. 2019;40:1314–1321. DOI: 10.1038/s41401-019-0230-z.
109. Deng J, Zhang N, Wang Y, Yang C, Wang Y, Xin C, Zhao J, Jin Z, Cao F, Zhang Z. FNDC5/irisin improves the therapeutic efficacy of bone marrow-derived mesenchymal stem cells for myocardial infarction. *Stem Cell Res Ther*. 2020;11:228. DOI: 10.1186/s13287-020-01746-z.
110. Zhong JC, Basu R, Guo D, Chow FL, Byrns S, Schuster M, Loibner H, Wang X-H, Penninger JM, Kassiri Z, et al. Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. *Circulation*. 2010;122:717–728. DOI: 10.1161/CIRCULATIONAHA.110.955369.
111. Ainscough JF, Drinkhill MJ, Sedo A, Turner NA, Brooke DA, Balmforth AJ, Ball SG. Angiotensin II type-1 receptor activation in the adult heart causes blood pressure-independent hypertrophy and cardiac dysfunction. *Cardiovasc Res*. 2009;81:592–600. DOI: 10.1093/cvr/cvn230.
112. Li R, Wang X, Wu S, Wu Y, Chen H, Xin J, Li HE, Lan J, Xue K, Li X, et al. Irisin ameliorates angiotensin II-induced cardiomyocyte apoptosis through autophagy. *J Cell Physiol*. 2019;234:17578–17588. DOI: 10.1002/jcp.28382.
113. Geng Z, Fan WY, Zhou B, Ye C, Tong Y, Zhou YB, Xiong XQ. FNDC5 attenuates obesity-induced cardiac hypertrophy by inactivating JAK2/STAT3-associated inflammation and oxidative stress. *J Transl Med*. 2019;17:107. DOI: 10.1186/s12967-019-1857-8.
114. Chen RR, Fan XH, Chen G, Zeng GW, Xue YG, Liu XT, Wang CY. Irisin attenuates angiotensin II-induced cardiac fibrosis via NRF2 mediated inhibition of ROS/TGFBETA1/SMAD2/3 signaling axis. *Chem Biol Interact*. 2019;302:11–21.
115. Li R-L, Wu S-S, Wu Y, Wang X-X, Chen H-Y, Xin J-J, Li HE, Lan J, Xue K-Y, Li X, et al. Irisin alleviates pressure overload-induced cardiac hypertrophy by inducing protective autophagy via mtor-independent activation of the AMPK-ULK1 pathway. *J Mol Cell Cardiol*. 2018;121:242–255. DOI: 10.1016/j.yjmcc.2018.07.250.
116. Liu X, Mujahid H, Rong B, Lu Q-H, Zhang W, Li P, Li NA, Liang E-S, Wang QI, Tang D-Q, et al. Irisin inhibits high glucose-induced endothelial-to-mesenchymal transition and exerts a dose-dependent bidirectional effect on diabetic cardiomyopathy. *J Cell Mol Med*. 2018;22:808–822. DOI: 10.1111/jcmm.13360.
117. Zhang X, Hu C, Kong CY, Song P, Wu HM, Xu SC, Yuan YP, Deng W, Ma ZG, Tang QZ. FNDC5 alleviates oxidative stress and cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity via activating AKT. *Cell Death Differ*. 2020;27:540–555. DOI: 10.1038/s41418-019-0372-z.
118. Tan Y, Ouyang H, Xiao X, Zhong J, Dong M. Irisin ameliorates septic cardiomyopathy via inhibiting drp1-related mitochondrial fission and normalizing the JNK-LATS2 signaling pathway. *Cell Stress Chaperones*. 2019;24:595–608. DOI: 10.1007/s12192-019-00992-2.
119. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP; American College of Sports M. American college of sports medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43:1334–1359. DOI: 10.1249/MSS.0b013e318213fefb.
120. Scharhag-Rosenberger F, Meyer T, Wegmann M, Ruppenthal S, Kaestner L, Morsch A, Hecksteden A. Irisin does not mediate resistance training-induced alterations in resting metabolic rate. *Med Sci Sports Exerc*. 2014;46:1736–1743. DOI: 10.1249/MSS.0000000000000286.
121. Agh F, Mohammadzadeh Honarvar N, Djalali M, Nematipour E, Gholamhoseini S, Zarei M, Ansari S, Javanbakht MH. Omega-3 fatty acid could increase one of myokines in male patients with coronary artery disease: a randomized, double-blind, placebo-controlled trial. *Arch Iran Med*. 2017;20:28–33.
122. Celik HT, Akkaya N, Erdamar H, Gok S, Kazanci F, Demircelik B, Cakmak M, Yigitoglu R. The effects of valsartan and amlodipine on the levels of irisin, adropin, and perilipin. *Clin Lab*. 2015;61:1889–1895. DOI: 10.7754/Clin.Lab.2015.150420.
123. Gouni-Berthold I, Berthold HK, Huh JY, Berman R, Spenrath N, Krone W, Mantzoros CS. 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. DOI: 10.1371/journal.pone.0072858.
124. Bi J, Zhang J, Ren Y, Du Z, Zhang Y, Liu C, Wang Y, Zhang L, Shi Z, Wu Z, et al. Exercise hormone irisin mitigates endothelial barrier dysfunction and microvascular leakage-related diseases. *JCI Insight*. 2020;5:e136277. DOI: 10.1172/jci.insight.136277.
125. Kim H, Wrann CD, Jedrychowski M, Vidoni S, Kitase Y, Nagano K, Zhou C, Chou J, Parkman VA, Novick SJ, et al. Irisin mediates effects on bone and fat via alphav integrin receptors. *Cell*. 2018;175:1756–1768 e1717.
126. Farmer SR. Boning up on irisin. *N Engl J Med*. 2019;380:1480–1482. DOI: 10.1056/NEJMcibr1900041.
127. Bi J, Zhang J, Ren Y, Du Z, Li T, Wang T, Zhang L, Wang M, Wu Z, Lv Y, et al. Irisin reverses intestinal epithelial barrier dysfunction during intestinal injury via binding to the integrin alphavbeta5 receptor. *J Cell Mol Med*. 2020;24:996–1009.
128. Chen K, Xu Z, Liu Y, Wang Z, Li YU, Xu X, Chen C, Xia T, Liao Q, Yao Y, et al. Irisin protects mitochondria function during pulmonary ischemia/reperfusion injury. *Sci Transl Med*. 2017;9:eaao6298. DOI: 10.1126/scitranslmed.aao6298.
129. Xie C, Zhang Y, Tran TDN, Wang H, Li S, George EV, Zhuang H, Zhang P, Kandel A, Lai Y, et al. Irisin controls growth, intracellular Ca2+ signals, and mitochondrial thermogenesis in cardiomyoblasts. *PLoS One*. 2015;10:e0136816. DOI: 10.1371/journal.pone.0136816.
130. Lv J, Pan Y, Li X, Cheng D, Ju H, Tian J, Shi H, Zhang Y. Study on the distribution and elimination of the new hormone irisin in vivo: new discoveries regarding irisin. *Horm Metab Res*. 2015;47:591–595. DOI: 10.1055/s-0035-1547261.
131. Jiang S, Oh DS, Dorotea D, Son E, Kim DS, Ha H. Dojuksan ameliorates tubulointerstitial fibrosis through irisin-mediated muscle-kidney crosstalk. *Phytomedicine*. 2021;80:153393. DOI: 10.1016/j.phymed.2020.153393.
132. Badr EA, Mostafa RG, Awad SM, Marwan H, Abd El-Bary HM, Shehab HE, Ghanem SE. A pilot study on the relation between irisin single-nucleotide polymorphism and risk of myocardial infarction. *Biochem Biophys Rep*. 2020;22:100742. DOI: 10.1016/j.bbrep.2020.100742.