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Review Article

Research Progress in the Cardiovascular Disease field Involving Irisin

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Abstract

Fibronectin type III Domain-containing 5 (FNDC5) is a precursor of Irisin. In skeletal muscle, the transcriptional coactivator PPAR-γ Coactivator-1α (PGC1-α) stimulates FNDC5 expression through biological reactions. FNDC5 is a membrane protein that is cleaved and secreted as irisin, a newly identified hormone. Irisin plays a critical role in modulating body metabolism, thermogenesis, and oxidative stress reduction. In recent years, studies on Irisin have increasingly emerged in the rapidly advancing field of cardiovascular diseases. This review summarizes recent findings on the correlation between irisin and cardiovascular diseases (such as lipid metabolism, acute myocardial infarction, heart failure, myocardial remodeling, blood pressure regulation and biomarkers, etc.), and outlines future research directions.

Introduction

Irisin, a recently discovered myokine and adipocytokine, regulates body metabolism, heat production, and oxidative stress reduction. The function of irisin is related mainly to energy balance and energy metabolism, and it has been proposed as a potential target for the treatment of obesity and metabolic diseases [1]. Global research efforts in recent years have uncovered additional functions of irisin. Irisin is considered a potential nonspecific biomarker. Scholars, from the initial focus on its role in glucose and fat metabolism, have expanded to many systems. These include inflammatory reactions (e.g., inhibition of TNF-α, IL-6, and other cytokines) [2], diabetes (protection of the secretory function of islet B cells, promotion of islet cell proliferation and insulin resistance through the ERK and P38 MAPK signaling pathways), neurological diseases [3] (Alzheimer's disease, acute brain injury), cardiovascular and cerebrovascular diseases (acute myocardial infarction, acute cerebral infarction), hypertension (promoting the release of NO by endothelial cells), hyperlipidemia (fat metabolism), acute lung injury (through the protective effect on mitochondria), etc. In the physiological and pathological process of the above systems, irisin is used for the diagnosis, treatment and prognosis of the related diseases described above. The present study reviews the structure and function of irisin and research on the role of irisin in cardiovascular disease.

Unlike previous reviews, this article provides a comprehensive synthesis of recent findings from 2020 to 2025, highlighting novel mechanistic insights, clinical correlations, and emerging controversies-particularly the dual role of irisin in blood pressure regulation and its translational relevance as a biomarker and therapeutic target.

Irisin was first found in the cells of skeletal muscle. It is expressed in almost all tissues and organs of eukaryotes [4]. Irisin is highly expressed in skeletal muscles and muscle-rich tissues (such as the pericardium and rectum), strongly expressed in the heart, and weakly expressed in the brain, kidney, liver, lung, and adipose tissue [5]. In addition, irisin is also expressed in gonad organs and the thyroid gland. Irisin can also be found in tissue and body fluids (such as plasma,cerebrospinal fluid, saliva, and milk) [6,7].

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Literature included in this review was selected based on relevance to irisin's role in cardiovascular disease, with a focus on peer-reviewed experimental and clinical studies published primarily between 2012 and 2025. Sources were identified through targeted searches in PubMed, Scopus, and Google Scholar using keywords such as 'irisin', 'cardiovascular disease', 'atherosclerosis', 'heart failure', 'blood pressure', and 'myocardial remodeling'.

Irisin with cardiovascular disease

Coronary atherosclerosis

Coronary Atherosclerosis (CA) accounts for over 17.5 million annual deaths globally according to recent data, as it is one of the main causes of human death, and atherosclerosis is the basis for the pathogenesis of CVD. Atherosclerosis involves multifactorial pathophysiological processes, such as vascular inflammation, endothelial dysfunction, oxidative stress, vascular smooth muscle cell activation, lipid infiltration, thrombosis, etc. [8]. Some studies have demonstrated that irisin is associated with coronary atherosclerosis and ACS. Higher serum irisin levels are associated with a lower burden of coronary atherosclerosis [5]. Moreover, the concentration of irisin in serum is related to atherosclerosis and acute myocardial infarction [9]. In an evaluation of Left Main Coronary Artery (LMCA) lesions via Intravascular Ultrasound (IVUS), serum irisin levels were found to be negatively associated with plaque lipid volume [10]. Compared with unstable coronary heart disease patients, patients with stable coronary heart disease have lower serum irisin levels [11].

Dyslipidemia: Dyslipidemia, a well-established metabolic risk factor and hallmark of atherosclerosis. Recent studies demonstrate that in addition to promoting white-to-brown adipose tissue conversion, administration of this hormone-like peptide in ApoE-deficient murine models limits intestinal cholesterol absorption while enhancing biliary cholesterol secretion and fecal excretion through upregulation of ABCG5/ABCG8 transporters and farnesoid X receptor activation [12]. Irisin reduces cholesterol, TC, glucose and FFA levels in obese mice via the cAMP/Protein Kinase A (PKA)/Hormone-sensitive Lipase (HSL)/perilipin pathway [13]. investigations reveal its lipid-lowering effects in obese mice involve cAMP/PKA/HSL/perilipin pathway-mediated reductions in total cholesterol, glucose, and free fatty acid levels. Furthermore, AMPK pathway activation with concurrent suppression of SREBP2 signaling has been shown to regulate hepatic and plasma cholesterol homeostasis [14]. Irisin significantly reduces atherosclerosis in apolipoprotein E-deficient mice by suppressing ox-LDL-induced cell inflammation and apoptosis [15]. While these findings underscore potential therapeutic applications in lipid metabolism disorders, the precise molecular interplay between cellular components, cytokine networks, and regulatory pathways remains to be fully elucidated.

Vascular inflammatory response: Irisin is highly expressed in the myocardium, with studies revealing that myocardial injury triggers a sharp elevation in its serum levels, correlating with injury severity and pathological progression in conditions such as acute myocardial infarction [9,16]. This myokine participates in the pathological process of coronary atherosclerosis through the inflammatory response and oxidative stress. Multiple inflammatory mediators (e.g., IL-6, TNF-α) and immune cell populations, including T lymphocytes and macrophages, contribute to vascular inflammatory responses. When this protein is applied in an apolipoprotein E-deficient diabetic mouse model, the mRNA expression levels of T lymphocytes, macrophages and inflammatory cells infiltrating the aortic plaques of mice are significantly reduced [17]. Further investigations demonstrate its efficacy in attenuating aortic atherosclerosis severity in hypercholesterolemic ApoE-deficient mice and suppressing carotid neointima formation following partial ligation, effects attributed to diminished vascular inflammation and apoptotic activity. Moreover, in a cell culture model, Irisin has been shown to inhibit the expression of inflammatory genes by downregulating the Reactive Oxygen Species (ROS)/p38 MAPK/NF-κB signaling pathway and to inhibit apoptosis by upregulating Bcl-2 and downregulating Bax and caspase-3 expression [15]. Notably, the molecule inhibits high glucose-induced apoptosis of HUVECs by increasing the expression of antioxidant enzymes, and these antioxidative stress effects are thought to be related to the activation of the phosphorylation of AMPK, Akt and eNOS [17].

Vascular repair: Vascular inflammation and various physical and chemical factors are important factors leading to damage of the vascular endothelium. The damage to and repair of blood vessels involves the entire pathological process of CVD. Vascular Endothelial Cells (VECs) play important roles in this pathological process [18]. Many pathophysiological effects (e.g., hypertension and dyslipidemia) can induce endothelial cell dysfunction, which has implications for the orchestration of inflammatory reactions, the regulation of redox balance, and thrombosis [19]. Irisin plays crucial roles in VEC proliferation, apoptosis and angiogenesis. Irisin promotes the proliferation of VECs through the ERK pathway and enhances the activity of VECs through the AKT/mTOR/S6K1/Nrf2 pathway, thereby stimulating angiogenesis and reducing vascular injury [20].

While the intrinsic link between VECs and irisin has been explored, Endothelial Progenitor Cells (EPCs) have also entered the scope of researchers. Endothelial progenitor cells (EPCs) are a group of circulating bone marrow-derived stem cells that have specific functions in neovascularization, vascular repair and endothelial regeneration [19]. EPCs and VECs form the «regenerative homeostasis» axis of the vascular system: EPCs act as reserve cells and transform into VECs during vascular injury to assist in repair; VECs regulate the mobilization and function of EPCs through paracrine signaling.Clinical trials have shown that the number of circulating EPCs in patients with coronary heart disease is reduced, which may negatively affect coronary endothelial repair function. In overweight children, serum Irisin levels are positively correlated with circulating EPCs levels [21]. In the pathological state of diabetes, this myokine may influence EPC function. Experiments revealed that treatment of diabetic mice with this exercise-induced cytokine significantly improved the expression and function

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of EPCs by activating the PI3K/Akt/eNOS signaling pathway. Moreover, this myokine can improve endothelial repair by promoting EPCs proliferation [22]. Although there are still many gaps in the research on irisin in the field of vascular repair, its potential deserves further exploration.

Heart failure

Approximately 2% of adults worldwide suffer from heart failure. The prevalence of heart failure increases with age, ranging from 1% of people under 55 years of age to more than 10% of people 70 years of age and older [23]. Hemodynamics, neurohormonal activation, inflammation, and oxidative stress are important drivers of heart failure [24]. Cardiomyocytes are cells with high metabolic energy, and mitochondria play a crucial role in their energy metabolism. The mitochondria in myocardial cells are regulated by various physiological factors. Exercise can increase the number of mitochondria in cells, affect changes in intracellular calcium ions, enhance the tricarboxylic acid cycle, and increase the content of NADH in cells, but exercise can also increase ROS. PGC-1α is involved in regulating the function of myocardial mitochondria and plays a role in regulating cardiac function [25]. In patients with advanced heart failure, the cardiomyocyte mitochondrial content density is markedly reduced [26]. PGC-1α induces expression of antioxidant enzymes, such as Superoxide Dismutase 2 (SOD2), which are important regulators of ROS metabolism in the mitochondria of myocardial cells. Moreover, studies have shown that PCG-1α downregulation of mitochondrial transcription factors leads to the occurrence of heart failure [27]. Irisin was identified as a PGC-1 α–dependent myokine [28]. Irisin can regulate glucose homeostasis in cells via the expression of UCP1. In another study, irisin improved cardiac remodeling by inhibiting oxidative stress and attenuating Akt signaling activation [29]. In summary, Irisin plays a role in the development of heart failure through oxidative stress and energy metabolism. These findings suggest this adipocytokine may be a new target for the treatment of heart failure.

Although irisin shows potential as a biomarker in various cardiovascular conditions, its clinical utility is limited by inconsistent assay methods, lack of standard reference ranges, and poor sensitivity and specificity across different cohorts. Additionally, fluctuations due to exercise, metabolic status, and circadian rhythm make it difficult to interpret serum levels in isolation, limiting its diagnostic reliability.

This bioactive protein molecule has potential for assessing the degree of heart failure and predicting the prognosis of patients with heart failure. In an acute myocardial injury combined with acute heart failure mouse model, increasing the serum concentration of Irisin increased mortality, possibly because this adipocytokine aggravated oxidative stress and increased myocardial oxygen consumption [30]. In another clinical study on Chronic Heart Failure (CHF), this molecule in the serum was lower in women and patients with cachexia than in other patients [31]. Another clinical study reported a significant decrease in serum this myokine levels in patients with Heart Failure with reduced Ejection Fraction (HFrEF) [32]. It is plausible to hypothesize that the observed alterations in serum irisin levels among CHF patients may correlate with Skeletal muscle content. Notably, a recent preliminary investigation into the pathophysiological interplay between this exercise-induced hormone and heart failure phenotypes revealed significantly elevated circulating irisin levels in patients with Heart Failure with preserved Ejection Fraction (HFpEF) compared to those with HFrEF [33]. However, the current long-term treatment measures for heart failure are still based on the activation and inhibition of neuroendocrine and antimyocardial remodeling and the ability to reduce the heart load. Through ongoing exploration by researchers, this multifunctional myokine has the potential to become a crucial target in the treatment or prediction of heart failure in the future.

Hypertension

There are 1.2 billion people worldwide with high blood pressure, and hypertension is known to be an important risk factor for the initiation of cardiovascular disease, which significantly increases the incidence of complications such as stroke, coronary heart disease, heart failure, and end-stage renal disease. Although hypertension is difficult to cure, it can be effectively controlled by changes in diet, exercise, and simple drug therapy, thereby reducing the risk of other major diseases. The impact of endocrine factors on the relationship between exercise and blood pressure regulation is still being explored. Regular long-term exercise can effectively control hypertension. Physical exercise can significantly increase the content of irisin in the serum, regardless of strenuous or chronic exercise. The retrospective analysis suggested that exercise-induced increases in irisin levels may be linked to skeletal muscle activity. A large amount of FNDC5, a precursor of irisin, is stored in skeletal muscle [34]. Multiple studies have revealed an association between this exercise-induced myokine levels and blood pressure. The levels of serum Irisin were negatively correlated with blood pressure in some studies. In patients with preeclampsia, this myokine expression is negatively correlated with blood pressure [35]. Peripherally applied irisin antagonizes the drug effect of phenylephrine hydrochloride via an endothelial mechanism, relaxes mouse mesenteric arteries, and decreases intra-arterial pressure [36]. In spontaneously hypertensive rats, administration of this exercise-induced myokine ameliorates endothelial dysfunction through the AMPK/Akt/eNOS/NO pathway, demonstrating antihypertensive efficacy [37]. Interestingly, in the aforementioned studies, this myokine was positively correlated with blood pressure changes in some specific situations. In patients with preeclampsia, FNDC5 expression in the placenta is positively correlated with blood pressure [35]. Upon reviewing early research papers, we observed contradictions in the correlation between Irisin and blood pressure. By focusing our search on animal studies and literature involving various intervention pathways, we uncovered some intriguing research reports. Injection of recombinant human Irisin into the third ventricle of rats activated neurons in the paraventricular nucleus of the hypothalamus, which increased blood pressure as well as cardiac contractility. In contrast, peripheral intravenous administration of this myokine, which activates

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ATP-sensitive potassium channels, dilates blood vessels and lowers blood pressure compared with those in controls [38]. However, in another study, the mechanism by which peripheral intravenous administration of Irisin decreased blood pressure in rats was through the inhibition of paraventricular nucleus neuron activation as well as oxidative stress. In a more recent study, it has been discovered that Irisin lowers blood pressure by activating the nrf2 signaling pathway within the paraventricular nucleus of the hypothalamus in spontaneously hypertensive rats [39]. In a clinical investigations in Idiopathic Pulmonary Arterial Hypertension (IPAH) patients demonstrate an inverse correlation between circulating levels of this exercise-responsive adipokine and pulmonary artery pressure, with lower concentrations predicting poorer clinical prognosis [40]. The effects of Irisin on blood pressure involve various points of action with different results. More exploration is needed to clarify the relationship between this adipocytokine and blood pressure, and it may serve as a potential target for the regulation of blood pressure in the future.

The contradictory findings regarding irisin's role in blood pressure regulation may stem from differences in experimental models, such as central versus peripheral administration routes, acute versus chronic exposure, or underlying comorbidities like diabetes and obesity. These factors may modulate irisin's interaction with hypothalamic neurons or vascular endothelium, resulting in divergent effects on systemic pressure.

Myocardial apoptosis and cardiac hypertrophy

With the aggravation of coronary heart disease, heart failure, and hypertension after not being effectively controlled, cardiac hypertrophy and myocardial apoptosis are inevitable. After reviewing a substantial body of literature, it was observed that myocardial apoptosis and remodeling are frequently associated with the activation of specific signaling pathways. Keywords such as Irisin, myocardial remodeling, and signaling pathways were indexed and systematically searched on PubMed to extract relevant research findings for reference. This exercise-induced myokine increases endothelial cell proliferation and protects cells from high glucose-induced apoptosis through activating Bcl-2 and Bax expression [41]. In a rat model of cardiac hypertrophy, endogenous Irisin levels were significantly decreased, while exogenous Irisin overexpression attenuated myocardial injury. In further cell experiments, this exercise-responsive adipokine was confirmed to protect against pressure overload-induced cardiac hypertrophy by inducing protective autophagy and autophagy flux via the activation of AMPK-ULK1 signaling [42]. In many animal and in vitro experiments, this myokine can alleviate cardiomyocyte apoptosis and myocardial remodeling in different physical and chemical environments through various pathways. In a myocardial hypertrophy rat model induced by Transverse Aortic Constriction (TAC), its can exert an inhibitory effect on myocardial remodeling by influencing the AMP-activated Protein Kinase (AMPK)-mammalian Target of Rapamycin (mTOR) signaling pathway, integrin signaling pathway, NOD-like Receptor Protein 3 (NLRP3), and pyroptosis cascade [43]. In the numerous animal experiments mentioned above, the molecule may affect myocardial remodeling through various pathways. However, the role of Irisin in the clinical treatment of myocardial remodeling needs to be supported by more studies. Despite promising preclinical outcomes, the therapeutic application of irisin remains constrained by an undefined therapeutic window, with both excessive and insufficient doses showing opposing physiological effects in some models. Most data to date are derived from rodent studies or in vitro experiments, which may not fully replicate human cardiovascular dynamics. Furthermore, inter-individual variability in irisin levels due to factors like exercise, gender, and metabolic state complicates clinical translation. Well-designed human trials are essential to determine dosing parameters, safety profiles, and long-term efficacy across diverse populations. Most existing studies evaluating irisin in cardiovascular contexts have been limited to single-center cohorts or animal models, with insufficient representation of ethnically or geographically diverse populations. To ensure generalizability and clinical relevance, future research should prioritize multi-center human trials across various demographic backgrounds.

Conclusion

Irisin has multiple physiological functions in the human body. In the field of non-cardiovascular diseases, this myokine participates in the regulation of energy balance and metabolism by promoting the conversion of white adipose tissue to brown adipose tissue. It can improve insulin resistance by regulating the genes and proteins related to glucose uptake and utilization. It is also associated with neural repair related to cognitive function. Irisin has a wide impact on cardiovascular diseases. It can affect the occurrence and development of coronary heart disease by regulating blood lipid metabolism, affecting the vascular inflammatory response and regulating vascular repair function. Modulating energy metabolism and oxidative stress influences heart failure pathology, which is expected to become a new exploration direction for the treatment of heart failure patients. Irisin has been shown to have beneficial antiapoptotic and antimyocardial remodeling effects. However, with respect to the effect of irisin on blood pressure, different intervention methods and different specific scenarios may lead to completely opposite conclusions. This review highlights studies demonstrating irisin's involvement in multiple signaling pathways to exert the above physiological effects (Table 1).

The function of irisin in the cardiovascular field is gaining interest, and many laboratories have investigated the therapeutic roles of irisin. The following areas could be further investigated:

1. The role of irisin in lipid metabolism and the vascular inflammatory response.
2. The role of irisin in the diagnosis and treatment of acute myocardial infarction.
3. Exploration of irisin as a therapeutic target for heart failure.

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Table 1: Number of studies showing that irisin can affect a variety of different signaling pathways to exert the above physiological effects.

Signaling Pathway	Target Cells/Tissues	Cardiovascular Effect	References
AMPK	Adipocyte,Endothelial cell,Cardiomyocyte	Lowering cholesterol levels, Antioxidative stress	[14,17,29]
PI3K/Akt/eNOS	Endothelial progenitor cells	Repairing endothelial cells	[22]
Nrf2	Paraventricular nucleus	inhibition of paraventricular nucleus neuron activation	[39]
AKT/mTOR/S6K1/Nrf2	Vascular endothelial cell	stimulating angiogenesis and reducing vascular injury	[20]
ROS/p38 MAPK/NF-κB	Endothelial cell	Inhibited the expression of inflammatory factors	[15]
AMPK/Akt/eNOS/NO	vascular endothelial cell	ameliorate endothelial dysfunction	[37]
AMPK/mTOR3	Cardiomyocyte	Improve cardiac remodeling	[43]
p38	Endothelial cell	Improve endothelial cell function	[41]
AMPK-ULK1	Cardiomyocyte	inducing protective autophagy and autophagy flux	[42]

4. The mechanism of irisin in cardiomyocyte apoptosis and myocardial remodeling.

5. Exploration of the regulatory mechanism of irisin on blood pressure.

6. Exploration of irisin as a biomarker for cardiovascular diseases.

Further research is warranted to identify more of the essential mechanisms and therapeutic effects of irisin in cardiovascular disease. As a new muscle factor, irisin has many unknown mechanisms in the field of cardiovascular diseases. Currently, limited studies have addressed irisin's role in cardiovascular diseases. Therefore, exploring the signaling pathways and genes involved in the diagnosis and treatment of cardiovascular diseases can provide a new approach for the prevention and treatment of these diseases.

In summary, irisin plays a multifaceted role in cardiovascular health by regulating lipid metabolism, vascular inflammation, endothelial repair, myocardial remodeling, and blood pressure modulation. Its effects are mechanistically mediated through key signaling pathways such as AMPK, Akt/eNOS, MAPK and mTOR, influencing oxidative stress response, mitochondrial function, and cellular proliferation. The signaling effects of irisin involve a coordinated hierarchy among AMPK, Akt, and MAPK pathways. AMPK acts as a metabolic master switch, often initiating downstream effects such as Akt phosphorylation, which promotes endothelial survival and nitric oxide synthesis via eNOS. In parallel, AMPK activation can inhibit MAPK-dependent pro-inflammatory cascades (e.g., p38 MAPK), thereby reducing oxidative stress. Furthermore, cross-talk between Akt and MAPK allows for context-specific regulation of apoptosis, angiogenesis, and autophagy. This integrative signaling supports irisin's cardioprotective effects through metabolic reprogramming, anti-inflammatory action, and vascular remodeling. Despite promising preclinical and clinical findings, several limitations persist, including inconsistencies in its effects across physiological models (e.g., conflicting blood pressure outcomes), a lack of standardized assays for irisin quantification, and insufficient data from large-scale, diverse human cohorts. Future research should prioritize longitudinal clinical trials, a deeper mechanistic dissection of pathway interactions, and the development of irisin-based interventions or biomarkers tailored to heterogeneous populations. These efforts will help clarify irisin's translational potential and support its integration into cardiovascular disease prevention and treatment strategies.

Author contributions

J.L. and W-H. P. wrote and edited the manuscript. Q.S. and J-J.J. critically reviewed the paper. Both authors have read and agreed to the published version of the manuscript.

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