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REVIEW ARTICLE

Fibronectin type III domain-containing 5 in cardiovascular and metabolic diseases: a promising biomarker and therapeutic target

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Cardiovascular and metabolic diseases are the leading causes of death and disability worldwide and impose a tremendous socioeconomic burden on individuals as well as the healthcare system. Fibronectin type III domain-containing 5 (FNDC5) is a widely distributed transmembrane glycoprotein that can be proteolytically cleaved and secreted as irisin to regulate glycolipid metabolism and cardiovascular homeostasis. In this review, we present the current knowledge on the predictive and therapeutic role of FNDC5 in a variety of cardiovascular and metabolic diseases, such as hypertension, atherosclerosis, ischemic heart disease, arrhythmia, metabolic cardiomyopathy, cardiac remodeling, heart failure, diabetes mellitus, and obesity.

Keywords: cardiovascular and metabolic diseases; FNDC5; biomarker; therapeutic target

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INTRODUCTION

Cardiovascular and metabolic diseases, including obesity, diabetes mellitus, and multiple cardiovascular injuries, are the leading causes of death and disability worldwide due to unhealthy behaviors, environmental toxins and genetic variants, and these conditions impose a tremendous socioeconomic burden on individuals and the healthcare system [1]. Despite improvements in health consciousness and medical practice, the prognosis of cardiovascular and metabolic diseases remains unsatisfactory, and effective interventions are still lacking.

Fibronectin type III domain-containing 5 (FNDC5) functions as a type I transmembrane glycoprotein to be proteolytically cleaved at the carboxy terminal to release irisin, which is mainly composed of the fibronectin III domain of FNDC5 [2]. FNDC5 was initially identified by two independent laboratories in 2002 and has attracted considerable attention since its definition as the precursor of an exercise-induced polypeptide myokine 10 years later [2–4]. Emerging studies have determined the wide distribution of FNDC5 in different body compartments, especially in those with high energy demand (e.g., the heart, adipose tissue, brain, liver, and skeletal muscle). Most of these studies demonstrated that FNDC5 is mainly expressed in skeletal muscle and adipose tissue; nevertheless, we recently detected a higher abundance of *Fndc5* mRNA in the heart than in skeletal muscle [2, 5–7]. In general, ~72% of circulating irisin is attributable to muscle secretion, while the remaining 28% appears from adipose tissue [2, 5]. Previous studies by us and other laboratories also revealed the pleiotropic roles of FNDC5 in regulating inflammation, oxidative stress, apoptosis, autophagy, angiogenesis, and mitochondrial function [6, 8–11]. However, its specific receptors remain elusive to date. Kim et al. reported that αV integrins are potential irisin receptors in osteocytes and fat cells and that chemical inhibition of αV integrins remarkably blocks signaling and function by irisin [12]. Irisin also interacts with transforming growth factor-beta type II receptor (TGFBR2) to activate the downstream mitogen-activated protein kinases, indicating TGFBR2 as a probable receptor for irisin [13]. In addition, some investigators proved that the biological functions of irisin might not depend on a receptor-mediated mode. Extracellular irisin can be taken up from circulation to lung cells via lipid raft-mediated endocytosis to prevent pulmonary ischemia–reperfusion (I/R) injury [10]. Moreover, the typical fibronectin III domain and plasma membrane distribution of FNDC5 strongly suggest its potential as a receptor for unidentified ligands [3]. With these findings in mind, FNDC5 was reported to be essential for regulating glycolipid metabolism and cardiovascular homeostasis under either basal or stress conditions [2, 14]. Liu et al. determined that FNDC5 deficiency causes lipid accumulation in the liver and increases serum nonesterified fatty acid levels under normal conditions [11]. FNDC5 overexpression or irisin treatment stimulate lipid oxidation and energy expenditure and decrease circulating free fatty acid concentrations at baseline [2, 15]. Li et al. found that neither overexpression nor knockout of FNDC5 affects growth or body weight and that plasma glucose and insulin levels are unaffected [16].

In this review, we characterize FNDC5 alterations in response to different cardiovascular and metabolic stresses to evaluate the predictive roles of these alterations in these diseases and summarize the biological functions of FNDC5 to determine its therapeutic value in cardiovascular and metabolic diseases.

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FNDC5 AND HYPERTENSION

Hypertension is a set of clinical and pathological syndromes and is characterized by the elevation of systolic and/or diastolic blood pressure [17]. Previous studies detected lower serum irisin levels in hypertensive patients and found that serum irisin levels negatively correlated with systolic/diastolic blood pressure [18–20]. In addition, the *FNDC5* single-nucleotide polymorphism (SNP) rs1746661 T-allele variant was reported to be associated with higher systolic blood pressure, while no correlation was found between the other two SNPs (rs16835198 and rs3480) and hypertension [21, 22]. Intriguingly, the antihypertensive drugs valsartan and amlodipine notably increased serum irisin levels after 12 weeks of treatment [20]. The hypothalamic paraventricular nucleus (PVN) is an important autonomic control center in the brain that regulates neurohormonal output and sympathetic tone. Balancing the inhibitory and excitatory neuronal inputs within the PVN is crucial to prevent sympathetic overdrive and hypertension [23, 24]. Huo et al. found that central irisin restored neurotransmitter balance in the PVN and decreased plasma norepinephrine concentrations, thereby reducing blood pressure [25]. Wang et al. also demonstrated the inhibitory effect of peripheral irisin on blood pressure in both control and spontaneously hypertensive rats. However, they stated that central administration of irisin into the third brain ventricle activates neurons in the PVN and increases blood pressure [22]. The endothelium, vascular smooth muscle, and adventitial fibroblasts coordinately orchestrate to maintain vascular homeostasis, whose dysfunction contributes to arterial stiffness and hypertension. Previous studies showed that circulating irisin positively correlates with endothelium-dependent vasodilation [26, 27]. Mechanistically, irisin activates endothelial nitric oxide synthase to increase nitric oxide production and stimulates transient receptor potential vanilloid subtype 4 channel-dependent extracellular calcium influx [28–32]. In addition, irisin promotes endothelium-independent vasodilation by inhibiting extracellular calcium influx and intracellular release in mesenteric arteries [33]. Phenotypic activation of vascular smooth muscle cells (VSMCs) and adventitial fibroblasts promotes extracellular matrix deposition, vascular remodeling, and arterial stiffness. Song et al. and Ling et al. revealed that irisin treatment significantly decreases the synthesis and secretion of matrix components, thereby preventing vascular remodeling and hypertension [9, 34]. Hyperhomocysteinemia is a crucial risk factor for arterial stiffness and hypertension, whereas circulating irisin is inversely associated with the serum homocysteine concentration [35]. Collectively, these data reveal FNDC5 as a novel biomarker and promising therapeutic target for hypertension.

FNDC5 AND ATHEROSCLEROSIS

Atherosclerosis is considered as a chronic inflammatory disease that is due to lipid metabolism disorder, endothelial injury, VSMC proliferation, monocyte adhesion, and foam cell formation, which then boosts matrix synthesis, artery calcification, wall thickening, luminal narrowing, and fibrous cap rupture and eventually causes thrombosis [36]. Circulating irisin levels are proven to be associated with the progression of vascular atherosclerosis and are regarded as an independent predictor for subclinical atherosclerosis [37–41]. Hisamatsu et al. observed a reverse correlation between serum irisin levels and artery calcification, and they also revealed that higher serum irisin levels correlated with a lower burden of coronary atherosclerosis [42]. These findings indicate a predictive role for FNDC5 expression in atherosclerosis. Dyslipidemia is one of the most important initiators of vascular injury and atherosclerosis, and FNDC5 plays an indispensable role in maintaining lipid homeostasis (reviewed in the "FNDC5 and obesity" section) [2, 11, 43]. In particular, apolipoprotein E (ApoE) is an important component of plasma lipoproteins required for normal lipoprotein metabolism and antiatherogenic regulation [44, 45]. Fuku et al. reported the association between *FNDC5* rs16835198 and the *APOE* ε2/ε4 allele; however, whether this association directly causes atherosclerosis needs further clarification [46]. Endothelial damage is another key determinant for atherosclerosis and a prerequisite for lipid deposition, monocyte adhesion, and intimal thickening [36]. FNDC5 directly promotes endothelial cell proliferation and suppresses cell apoptosis and vascular inflammation, thereby sustaining endothelial homeostasis [47, 48]. In addition, Zhu et al. found that FNDC5 improved the function of endothelial progenitor cells and helped with endothelial repair [49]. The accumulation of oxidized low-density lipoprotein (oxLDL) is the main pathogenic factor for endothelial injury, monocyte recruitment and foam cell formation [36]. A previous study showed that FNDC5 alleviates oxLDL-induced endothelial inflammation, oxidative stress, and apoptosis, thereby preventing the development of atherosclerosis [50]. Monocytes, the predominant inflammatory cells during the development of atherosclerosis, are recruited to the subendothelial layer of the arterial wall, where they differentiate into macrophages and engulf oxidized lipoproteins to form foam cells [36]. In addition to proinflammatory cytokines, adhesion molecule upregulation is an important prerequisite for monocyte docking and infiltration. The results from Zang et al. indicated that FNDC5 suppressed the expression of vascular cell adhesion molecule-1 and inhibited monocyte adhesion to VSMCs [51]. However, higher irisin levels also caused E-selectin and intracellular adhesion molecule-1 upregulation in primary human umbilical vein endothelial cells [52]. VSMCs are another important source for foam cells, and a previous study showed that 45% of foam cells have a VSMC phenotype in advanced atherosclerosis lesions [53]. Zang et al. showed that FNDC5 treatment significantly inhibited oxLDL-mediated foam cell formation in VSMCs [51]. These studies clearly determine the antiatherogenic functions of FNDC5 and propose it as a potential therapeutic target.

FNDC5 AND ISCHEMIC HEART DISEASE

Ischemic heart disease remains the primary cause of death worldwide due to the induction of congestive heart failure and life-threatening arrhythmias. Timely blood flow restoration by percutaneous coronary intervention is an effective intervention to rescue viable cardiomyocytes, but it also causes additional I/R damage [54]. Previous studies indicated that circulating irisin is decreased in patients with either stable coronary artery disease (CAD) or myocardial infarction but gradually increases after coronary bypass surgery [55–59]. Moreover, Aydin et al. found a completely negative correlation between circulating irisin and "gold standard" levels (serum troponin I, creatine kinase isoenzymes, and creatine kinase). In addition to serum irisin, they revealed that saliva irisin also correlated with serum "gold standard" levels, defining irisin as a new and perhaps noninvasive biomarker for patients with acute myocardial infarction [60]. Infarcted patients with lower serum irisin levels had more severe fibrotic remodeling, cardiac dysfunction and an increased risk for adverse cardiovascular outcomes [61–63]. In contrast, two studies reported a positive association between serum irisin and the risk for major adverse cardiovascular events. The authors explained that the higher serum irisin levels represent an irisin-resistant status with increased cardiovascular and metabolic risks or are a direct result due to severe muscle damage [64, 65]. Reactive oxygen species (ROS) overproduction promotes oxidative damage to biomacromolecules and triggers cardiomyocyte apoptosis [66]. Mitochondria are the major source of ROS within the myocardium. Previous studies suggested that FNDC5 targets mitochondria and interacts with antioxidant molecules to prevent ROS overproduction and cardiomyocyte apoptosis during myocardial I/R injury [10, 67, 68]. Surprisingly, excessive irisin increases mitochondrial ROS generation and aggravates cardiomyocyte apoptosis in a

hypoxic environment [69]. Microvessel angiogenesis is a possible cardioprotective mechanism for ischemic heart disease, and we previously showed that revascularization is essential for the repair of infarcted myocardium [70]. FNDC5 markedly promotes the proliferation of vascular endothelial cells and increases microvessel density, thereby protecting against ischemic heart disease [8, 71]. Cardiac progenitor cells have been show to be the specific regenerative cell source within the heart and have beneficial effects on cardiac regeneration and neovascularization [72]. Zhao et al. found that irisin pretreatment enhances the protective capacity of cardiac progenitor cells in terms of myocardial repair and functional improvement in the infarcted heart [73]. In a randomized controlled trial, the investigators demonstrated that omega-3 fatty acid supplementation elevates serum irisin and then attenuates the inflammatory response as well as lipid metabolism dysfunction in male CAD patients [74]. Iloprost and sildenafil are the two pharmacological agents for blood supply restoration and reoxygenation via vasodilatation during ischemic conditions. Aydin et al. proved that irisin elevation by individual or combined administration of iloprost and sildenafil contributes to wound recovery and cardioprotection in myocardial infarction [75]. Overall, targeting FNDC5 may provide therapeutic value to patients with myocardial infarction.

FNDC5 AND ARRHYTHMIA

Arrhythmia is characterized by an abnormal heart rate and/or rhythm due to a disorder in electrical impulse origination and/or propagation [76]. Considering that athletes have higher irisin levels and lower resting heart rates, it is reasonable to conclude that FNDC5 is required to maintain a normal heart beat. The physical cardiac conduction depends on stable electrocardial activity, normal cardiac structure, and balanced autonomic nervous system. Sundarrajan et al. showed that exogenous irisin increases the heart rate, while irisin knockdown has the opposite effect [77]. Calcium participates in regulating cell membrane potential, which is essential for the repolarization of myocardial action potential and neuronal excitatory conduction. Xie et al. found that irisin treatment significantly increases intracellular calcium concentration via an irisin-specific membrane receptor in H9C2 cells [78]. In addition, irisin treatment induces an increase in cytosolic calcium levels and neuronal depolarization of nucleus ambiguus neurons, thereby evoking bradycardia in conscious rats [79]. FNDC5 also activates the NF-E2-related factor 2 (Nrf2) pathway in the hypothalamic PVN, decreases circulating norepinephrine levels, and effectively prevents sympathetic overdrive [25]. Normal cardiac architecture is pivotal for electrocardial conduction, whereas structural remodeling triggers electrical remodeling and the occurrence of arrhythmia. As mentioned later ("FNDC5 and cardiac remodeling"), various studies have revealed the protective effect of FNDC5 on cardiac hypertrophy and fibrotic remodeling. These data support the involvement of FNDC5 in arrhythmia, and further studies are needed to characterize its exact role and potential molecular basis under pathological conditions.

FNDC5 AND METABOLIC CARDIOMYOPATHY

Metabolic cardiomyopathy develops under the context of systemic metabolic disorders that are characterized by structural and functional alterations without CAD or hypertension. Hyperglycemia or hyperlipidemia-induced metabolic disturbance triggers chronic low-grade inflammation within the heart, which subsequently provokes oxidative injury, endoplasmic reticulum stress, mitochondrial dysfunction, cardiomyocyte apoptosis, and fibrotic remodeling, thereby leading to impairment of both diastolic and systolic functions [80]. Consistently, our previous studies revealed that the attenuation of inflammation, oxidative stress, and cardiomyocyte apoptosis by either genetic or pharmacological methods significantly improved cardiac dysfunction in response to diabetes mellitus or obesity [81–83]. The results from Stratigou et al. showed that serum irisin levels are independently related to inflammation, insulin resistance, and other cardiovascular and metabolic risk factors [84]. Moreover, FNDC5 overexpression remarkably diminished obesity-induced cardiac inflammation, oxidative stress, and hypertrophic remodeling [85]. Excessive lipid accumulation within the myocardium causes lipotoxicity and promotes myocardial inflammation, oxidative damage, and cardiomyocyte apoptosis. Interestingly, irisin incubation counteracts lipotoxicity and cardiomyocyte apoptosis [86]. Cardiac fibrosis is a key feature of metabolic cardiomyopathy and contributes to congestive heart failure and lethal arrhythmia. Endothelial-to-mesenchymal transition functions as an important source of cardiac fibroblasts and plays an indispensable role in fibrotic remodeling in the context of metabolic dysfunction [87]. We previously showed that inhibiting endothelial-to-mesenchymal transition significantly ameliorates fibrotic remodeling and cardiac dysfunction [88, 89]. Liu et al. proved the inhibitory role of FNDC5 in the high glucose-induced endothelial-to-mesenchymal transition and the cardioprotective effect during diabetic cardiomyopathy. Unexpectedly, they also found that high-dose irisin treatment accelerates the proliferation and migration of cardiac fibroblasts, thereby resulting in excessive collagen deposition and cardiac dysfunction [90]. Autophagy disorder is responsible for the initiation and progression of diabetic cardiomyopathy, and we previously showed that autophagy restoration notably decreases inflammation, oxidative stress, apoptosis, and cardiac dysfunction in diabetic hearts [91, 92]. Liu et al. demonstrated that *Fndc5* overexpression prevents and that *Fndc5* deficiency exacerbates autophagy impairment and lipid accumulation [11]. In contrast to the extensive effects of visceral adipose tissue (VAT) on the whole body, epicardial fat is physically next to the myocardium and shares the same microcirculation that is important for cardiac regulation [93]. Increased epicardial fat volume independently correlates with myocardial fat accumulation, fibrosis, and cardiac dysfunction in the context of metabolic disturbance [94, 95]. Previous studies have shown a significant association between circulating irisin and epicardial fat; however, more thorough studies are required to further dissect the underlying mechanisms [96, 97]. These results reveal the beneficial effect of FNDC5 against metabolic cardiomyopathy.

FNDC5 AND CARDIAC REMODELING

Cardiac remodeling is characterized by cardiomyocyte hypertrophy and interstitial fibrosis upon various cardiac stresses, leading to both enhanced myocardial stiffness and compromised cardiac contractility [98]. Under pathological conditions, cardiomyocyte hypertrophy occurs as an adaptive response to incremental biomechanical loads after the activation of a series of hypertrophic pathways. Beyond the cardiomyocyte-centric view, cardiac fibroblasts are involved in orchestrating fibrotic remodeling of the heart by regulating myocardial collagen turnover [87, 98]. Cardiac remodeling is an independent risk factor for heart failure, arrhythmia, and sudden death and serves as a key determinant of the clinical course and long-term outcome of patients with cardiovascular diseases [98]. Our previous studies provide further understanding of the pathogenesis of cardiac remodeling, and these data suggest that inhibiting cardiac remodeling by either pharmacological or genetic methods notably improves cardiac dysfunction and survival [99–103]. Bashar et al. revealed a negative correlation between the serum irisin level and myocardial collagen volume in infarcted hearts [62]. Further studies revealed that irisin treatment activates Nrf2 and suppresses the ROS/TGF-β/Smad pathway in cardiac fibroblasts, which

subsequently blunts collagen synthesis and fibroblast-myofibroblast transformation [104]. In addition, irisin administration promotes angiogenesis in the infarct border zone and thus reduces cardiac fibrosis and ventricular dilation [8]. Smad3 is the best-known fibrogenic transcriptional factor that directly mediates myofibroblast activation and fibrotic response, and we previously showed that Smad3 inhibition significantly alleviates myofibroblast activation and cardiac fibrosis [105, 106]. Tiano et al. identified a putative Smad3 binding site in the *Fndc5* promoter, and Smad3 activation decreased FNDC5 expression, indicating the connection between FNDC5 and Smad3 [107, 108]. A further study by Peng et al. proved that irisin interacts with TGFBR2 to interfere with its recruitment to TGFBR1, thereby preventing Smad3 activation and fibrogenesis [13]. In addition, irisin treatment inhibits the high glucose-induced endothelial-to-mesenchymal transition and has a cardioprotective effect on fibrotic remodeling in diabetic hearts [90]. FNDC5 also participates in the regulation of pathological cardiac hypertrophy. Li et al. proved that FNDC5 provokes a protective autophagy flux by activating 5′ AMP-activated protein kinase (AMPK)/Unc-51-like kinase 1 signaling to alleviate pressure overload-induced cardiac hypertrophy, whereas Yu et al. found that the antihypertrophic effect of FNDC5 might be attributed to AMPK-mediated mammalian target of rapamycin suppression in a pressure overload-induced hypertrophic model [16, 109]. In addition, Geng et al. suggested that FNDC5 prevents obesity-induced cardiac hypertrophy by decreasing intramyocardial inflammation and oxidative stress [85]. These studies reveal FNDC5 as a promising therapeutic target for cardiac remodeling.

FNDC5 AND HEART FAILURE

Heart failure is the common end stage of various cardiovascular diseases and places a heavy burden on individuals, families and society as a whole. Currently, no reliable biomarkers (except N-terminal pro-brain natriuretic peptide, NT-proBNP) or effective therapeutic strategies are available for failing hearts [110]. As indicated in the above context, FNDC5 significantly improves cardiac dysfunction under different pathological conditions and prevents undesirable cardiac remodeling. Previous studies suggested that patients with heart failure have decreased serum irisin levels, especially in heart failure with reduced ejection fraction [63, 111]. Some investigators explained that the reduced irisin levels might be ascribed to inflammation or protein energy wasting instead of volume overload [112, 113]. A previous study demonstrated that infarcted patients with higher circulating irisin were more likely to develop heart failure and adverse cardiovascular outcomes [65]. In addition, serum irisin levels positively correlate with circulating BNP, the New York Heart Association class and 1-year all-cause mortality [114, 115]. More importantly, the results from Shen et al. confirm that serum irisin concentrations have a better prognostic value for acute heart failure than NT-proBNP [115]. Considering the beneficial effects of FNDC5, we thought higher circulating irisin might indicate an irisin-resistant status or a more severe cardiac injury. In addition, FNDC5 expression in skeletal muscle also correlates with the aerobic performance of heart failure patients [116]. These data suggest that FNDC5 could be regarded as a promising biomarker and therapeutic target for heart failure.

FNDC5 AND OTHER CARDIOVASCULAR DISEASES

Doxorubicin remains the cornerstone of tumor chemotherapy regimens; however, its therapeutic value is extremely hampered by its cardiotoxicity. Inflammation, oxidative stress, and cardiomyocyte apoptosis are responsible for doxorubicin-elicited cardiac dysfunction [117]. Our previous studies confirmed that inhibiting these pathogenic factors markedly protects against doxorubicin-induced acute or chronic cardiotoxicity [66, 118–121]. Aydin et al. found that myocardial and serum irisin levels are upregulated in doxorubicin-treated rats, while we recently proved that doxorubicin treatment notably suppresses FNDC5 expression in murine hearts and H9C2 cells. Moreover, cardiomyocyte-specific FNDC5 overexpression or irisin infusion alleviates oxidative stress and cardiomyocyte apoptosis, thereby preventing doxorubicin-induced cardiac dysfunction [6, 122].

Septic cardiomyopathy is a common complication in patients with severe sepsis, manifesting as reversible cardiac depression and ventricular dilation [123]. We previously reported that restraining inflammation, apoptosis, and pyroptosis significantly prevent the progression of septic cardiomyopathy [124–126]. However, mitochondrial fission also contributes to septic cardiomyopathy by provoking mitochondrial fragmentation, oxidative damage, and apoptosis. Tan et al. observed that irisin treatment prevents mitochondrial fission and dysfunction, thereby ameliorating septic cardiomyopathy [127]. Lipopolysaccharide (LPS) is a main component of the outer membrane in gram-negative bacteria and functions as the major inducer of septic cardiomyopathy. A previous study observed that individuals with high circulating irisin have significantly lower serum LPS concentrations [128].

In addition, FNDC5 might also be implicated in the pathogenesis of cardiac dysfunction among hemodialysis patients. Kałużna et al. observed that serum irisin level negatively correlates with right ventricular diameter and identified it as a potential prognostic biomarker of cardiac status in hemodialysis patients [129].

FNDC5 AND DIABETES MELLITUS

Diabetes mellitus is a clinically heterogeneous endocrine/metabolic disorder caused by insulin deficiency or resistance, and no specific biomarkers or therapeutic strategies are available to date [130]. Many studies detected lower serum irisin levels in patients with type 2 diabetes mellitus (T2DM) that were further reduced with the progression of glucose intolerance [27, 129, 131–134]. In addition, Choi et al. demonstrated that higher irisin levels were associated with lower odds of prevalent newly diagnosed T2DM, suggesting a protective effect of irisin against T2DM [135]. However, a small number of researchers observed an increased serum irisin level in T2DM patients, and they attributed this elevation to a probable irisin-resistant status or a compensatory mechanism to improve glucose intolerance [52, 136–138]. In contrast to the decreased irisin level in T2DM patients, circulating irisin was increased in T1DM patients compared with nondiabetic control subjects [139–141]. This discrepancy was deemed to be a result of the distinct insulin levels in different types of diabetes mellitus. They demonstrated a negative correlation between circulating irisin and serum insulin levels and that increased irisin concentrations compensated for the reduced insulin levels [136, 139, 142, 143]. Some investigators also proved that serum irisin levels predict the status of inflammation, oxidative stress, glucose homeostasis, and insulin sensitivity in diabetic animals or patients, which confirms the predictive role of FNDC5 in diabetes mellitus [128, 137, 144, 145].

Many direct or indirect effects of FNDC5 on glucose regulatory mechanisms in different organs are required for its protection against insulin resistance and diabetes mellitus, which is reviewed in detail by Perakakis et al. [14]. In this review, we briefly summarized the role of FNDC5 in insulin regulation and glycometabolic processes. Previous studies determined that circulating irisin correlates with pancreatic β-cell function and that irisin treatment significantly improves glucolipotoxicity-associated β-cell apoptosis and insulin reduction [146–148]. In addition, Guo et al. showed that plasma free fatty acid-mediated FNDC5 downregulation elicits insulin resistance, whereas irisin supplementation can restore insulin sensitivity [15, 149]. Glucose uptake

is the first step and a prerequisite for normal glycometabolic processes. It is well known that glucose uptake depends on the upregulation and membrane translocation of glucose transporter 4 (GLUT4). Many studies have suggested that FNDC5 increases GLUT4 expression and membrane translocation, thereby promoting glucose uptake in adipocytes and muscle cells [150–153]. In addition, FNDC5 enhances the abundance of lactate dehydrogenase A and pyruvate dehydrogenase kinase 1 (two crucial enzymes in glycolysis) to accelerate aerobic glycolysis [13, 154]. Hepatic gluconeogenesis is a key source of blood glucose, and some investigators observed an inhibitory effect of FNDC5 on gluconeogenesis [153, 155]. FNDC5 also suppresses the enzymes for glycogenolysis (glycogen phosphorylase) and enhances the enzymes for glycogen synthesis (glycogen synthase), thereby decreasing blood glucose [150, 155]. Moreover, several studies have reported the synergistic effects of irisin and other hormones in maintaining glucose homeostasis, such as betatrophin (also known as angiopoietin-like protein 8) and leptin [156, 157].

There are some specific types of diabetes mellitus, including gestational diabetes mellitus (GDM) and polycystic ovarian syndrome (PCOS). Previous studies observed that serum irisin concentrations are markedly increased in pregnant women but decreased in GDM patients, as is irisin in breast milk [158–163]. The authors of those studies suggest that irisin upregulation is a compensatory response to energy imbalance and hormone disorder during pregnancy and that decreased irisin exacerbates GDM progression [164, 165]. Of note, serum irisin downregulation in pregnant women correlates with an increased risk for GDM progression and can be identified as an early biomarker to predict later development of GDM [166, 167]. PCOS is a complex and heterogeneous disease that is frequently accompanied by insulin resistance [168]. In PCOS patients, most investigators detected an elevation in circulating irisin that might be secondary to insulin-resistant conditions or hyperandrogenism [143, 169–172]. Accordingly, Li et al. demonstrated that metformin treatment for 6 months improved insulin resistance and subsequently decreased serum irisin levels in PCOS patients [173]. Several studies observed that circulating irisin is downregulated in PCOS patients and that the reduction in granulosa cells exacerbates metabolic disturbance [174–176]. Circulating irisin in PCOS patients is also closely correlated with body fat content, bone mineral density, endometrial receptivity, and metabolic homeostasis [175, 177–179].

In addition, *FNDC5* SNPs play an important role in regulating multiple metabolic processes, especially glucose homeostasis. Despite being rarely seen in patients with T2DM or diabetic nephropathy, the rs16835198 T allele significantly decreases T2DM prevalence among Egyptians [180]. Conversely, the rs16835198 G allele has insulin desensitizing action and causes increases in glycated hemoglobin and fasting plasma glucose [180–182]. *FNDC5* SNP rs16835198 was reported to correlate with pancreatic β-cell function and glycometabolism; however, it does not affect fasting insulin levels [182, 183]. Moreover, the rs3480 G allele and rs726344 A allele were found to be linked to severe insulin resistance, whereas the T allele of rs1746661 correlates with higher systolic blood pressure and dyslipidemia among women with T2DM [21, 181, 182, 184]. A previous study found that the *FNDC5* rs157069 T allele notably decreases insulin sensitivity by downregulating serum irisin levels and further promotes the development of proliferative diabetic retinopathy in a Chinese population [137, 185]. These results support the important role of FNDC5 expression and genetic SNPs in diabetes mellitus, including GDM and PCOS.

FNDC5 AND OBESITY

Obesity has been shown to be an increasing global public health concern and serves as a predisposing factor for various cardiovascular and metabolic diseases [82, 186]. FNDC5 is widely distributed in different human tissues, especially adipose tissue, and helps to maintain normal lipid metabolism [5, 187]. Most studies found that circulating irisin levels and tissue FNDC5 expression are higher in obese patients but lower in normal-weight control subjects or anorexic individuals [188–192]. Human adipose tissue is a primary source of FNDC5, and adipocytes in VAT or subcutaneous adipose tissue (SAT) from overweight patients produce more irisin than those from healthy control subjects [5, 193, 194]. In addition, Gao et al. reported that irisin incubation further promotes irisin secretion from adipocytes by upregulating FNDC5 expression in an autocrine manner [195]. We reasonably speculate that this positive feedback helps to elevate circulating irisin levels in obese patients. However, some other studies reported conflicting results. Moreno-Navarrete et al. showed that circulating irisin and FNDC5 gene expression in adipose tissue or muscle are significantly decreased in association with obesity [196]. In addition, a reduction in serum irisin levels and FNDC5 expression within the brain has been observed in animals fed a high-fat diet [197, 198]. The discrepancy might be ascribed to the heterogeneity of subjects in these studies, as some studies included obese patients with metabolic syndrome who had decreased circulating irisin levels due to impaired beige adipogenesis [199, 200].

Generally, increased circulating irisin independently predicts a higher risk of obesity and positively correlates with adiposity indices, including body mass index, waist circumference, fat mass, and lipid profile [201–204]. Interestingly, previous studies indicated that higher irisin expression helps to maintain the homeostasis of lipid metabolism [2, 11, 205, 206]. These studies proved that FNDC5 overexpression or irisin treatment drives adipocyte browning and lipid oxidation and suppresses adipogenesis and cholesterol synthesis, thereby improving whole body energy expenditure and obesity [43, 207–211]. In addition, FNDC5 overexpression delays the accumulation and M1 polarization of macrophages in adipose tissue and reduces local inflammation to inhibit obesity progression [212–214]. Moreover, central or peripheral irisin treatment significantly suppresses food intake and energy input [215–217]. *FNDC5* SNPs are also involved in the pathogenesis of obesity and its complications. The results from Todendi et al. and others demonstrated that the rs726344 G allele and rs16835198 T-allele variants increase susceptibility to obesity [218, 219]. Two additional studies reported an association of the *FNDC5* rs3480 G allele with hepatic steatosis and fibrotic remodeling [220, 221]. Considering these beneficial effects of FNDC5 on obesity, we speculate that FNDC5 upregulation acts as a compensatory mechanism for the increased fat storage and energy expenditure impairment.

Various pharmacological, nonpharmacological, or even surgical interventions are advised to increase circulating or local FNDC5 production and then improve abnormal lipid profiles together with obesity. Consistent with its powerful effect on FNDC5 upregulation and weight loss, kinesitherapy exercise has been proposed as a first-line strategy against obesity and relevant complications. Previous studies observed an increased circulating irisin level in obese subjects with different training modes, and Kartinah et al. further determined that exercise enhances irisin uptake from circulation into adipose tissue, where it maintains lipid homeostasis [222–225]. Obesity is an independent risk factor for other cardiovascular and metabolic diseases that are notably prevented by exercise-induced FNDC5 in our aforementioned parts. Kang et al. also reported that swimming effectively elevates circulating irisin and bone FNDC5 levels and improves obesity-elicited osteoporosis [226]. Intriguingly, compensatory upregulation of FNDC5 in overweight subjects is reduced in parallel with body weight after hypocaloric dietary treatment, indicating an improved lipid profile [227–229]. Furthermore, oral administration of resveratrol upregulates FNDC5 expression in human SAT and

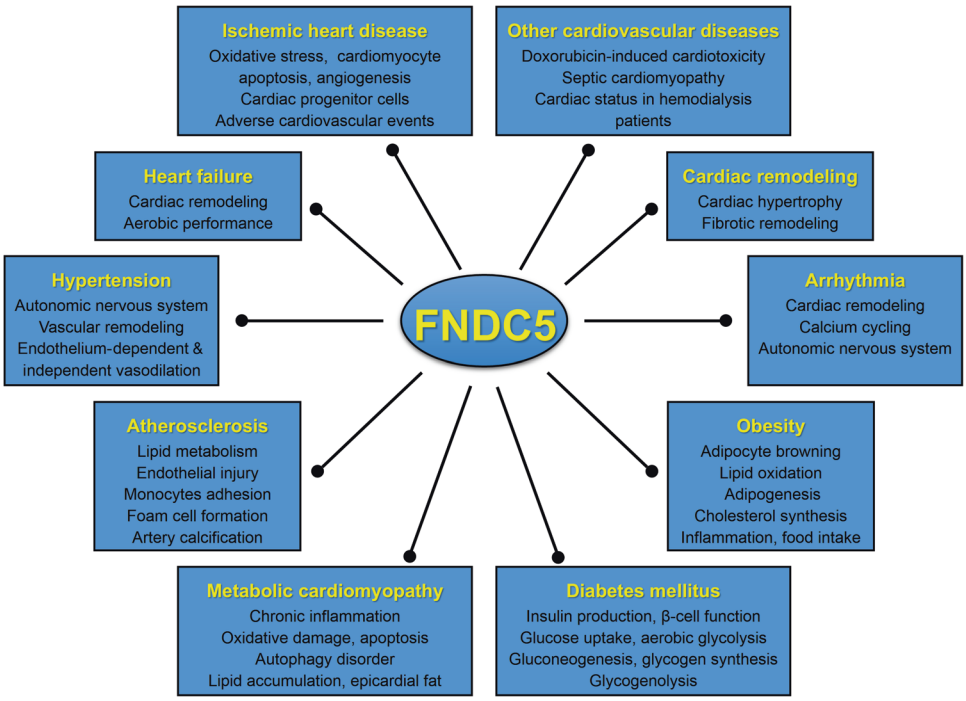

Fig. 1 FNDC5 has pleiotropic effects on cardiovascular and metabolic diseases. FNDC5 protects against these diseases by regulating multiple pathophysiological processes and serves as a promising biomarker and therapeutic target.

promotes adipocyte energy expenditure [230]. Of note, some investigators observed an alteration in circulating irisin in fatty patients after bariatric surgery, which is accompanied by significant weight loss and improved metabolic status [231–233]. These data provide a safe and efficacious intervention strategy that involves regulating FNDC5 expression to mitigate obesity in human subjects.

CONCLUSION AND PERSPECTIVE

FNDC5 has received considerable attention since its first description as the precursor of an exercise-induced polypeptide myokine, irisin, which shares 100% identity between mice and humans. FNDC5 is widely distributed in different body compartments, especially in tissues with high energy demand, and has protective effects against cardiovascular and metabolic disturbance. The current review summarizes the potential involvement of FNDC5 in cardiovascular and metabolic homeostasis, thereby defining FNDC5 as a promising biomarker and therapeutic target for cardiovascular and metabolic diseases (Fig. 1). Despite the detailed understanding of the role of FNDC5 in various pathophysiological processes, several questions remain to be answered. First, special antibodies for distinguishing FNDC5 and irisin are urgently required. Second, identifying the specific receptors for irisin and dissecting the possible action modes will be a large leap forward in this field. Third, an accurate splicing procedure from FNDC5 to irisin demands further clarification. Fourth, whether the functions of FNDC5 are realized by cleaved irisin or by FNDC5 itself should be thoroughly explored. Finally, inconsistencies in reported data highlight the necessity for more accurate and well-designed clinical studies to demonstrate the predictive and therapeutic role of FNDC5 in cardiovascular and metabolic diseases.

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ADDITIONAL INFORMATION

Conflict of interest: The authors declare that they have no conflict of interest.

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