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A review of fibroblast growth factor 21 in diabetic cardiomyopathy

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Abstract

FGF21 (fibroblast growth factor 21) is a regulator of metabolism and performs an important role in glucose and lipid metabolism and the maintenance of energy balance. FGF21 is principally expressed in the liver, but it can also be found in the pancreas, skeletal muscle, and adipose tissue. It is known that levels of serum FGF21 are significantly elevated in obese, insulin-resistant patients, and those with metabolic syndrome. Elevated levels of FGF21 in serum during the early stages of various metabolic diseases are considered a compensatory response by the organism. Therefore, FGF21 is considered a hormone in response to stress and an early diagnostic marker of disease. Diabetic cardiomyopathy is a special type of cardiac complication, characterized as a chronic myocardial disorder caused by diabetes. The pathological process includes increased oxidative stress, energy metabolism in myocardial cells, an inflammatory response, and myocardial cell apoptosis. A growing body of evidence suggests that FGF21 has the potential to be an effective drug for the treatment of diabetic cardiomyopathy. Here, we review recent progress on the characteristics of FGF21 in its protective role, especially in pathological processes such as suppressing apoptosis in the myocardium, reducing inflammation in cardiomyocytes, reducing oxidative stress, and promoting fatty acid oxidation. In addition, we explore the possibility that diabetic cardiomyopathy can be delayed through the application of FGF21, providing possible therapeutic targets of the disease.

Keywords FGF21 (fibroblast growth factor 21) · Diabetic cardiomyopathy · Oxidative stress · Myocardial cell energy metabolism · Collagen deposition · Inflammatory response · Apoptosis

Abbreviation

AGES	advanced glycosylation end-products
AMPK	adenosine 5′-monophosphate (AMP)-activated kinase
ATF6	activating transcription factor-6
BMI	body mass index
CERB	cAMP-response element-binding protein
CHOP	C/EBP homologous protein
DCM	diabetic cardiomyopathy
ERK	extracellular-regulated protein kinases
FAO	fatty acid oxidation
FFA	free fatty acid

Highlights: In this review, we have retrospectively analyzed the protective effects of FGF21 in the pathological process of diabetic cardiomyopathy. It represents a possible new strategy for the treatment of diabetic cardiomyopathy.

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HDL-c	high-density lipoprotein-c
HSCs	hepatic stellate cell
HSPG	heparan sulfate proteoglycan
ICAM-1	intercellular cell adhesion molecule-1
IRE-1	inositol-requiring protein-1
LDL-c	low-density lipoprotein-c
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MDA	malonaldehyde
NF-κB	nuclear factor κB
pERK	protein kinase R-like ER kinase
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator-1α
PI3K	phosphatidylinositol 3-kinase
PKC	protein kinase C
PPA	peroxisome proliferator-activated receptor
RAGEs	receptor for advanced glycation end products
Sirt1	silent information regulator-1
UPR	unfolded protein response
WT	wild type

Introduction

Structure and physiological functions of FGF21

Fibroblast growth factor (FGF) is a superfamily of cytokines that regulates cell growth, differentiation, and metabolism [1–4]. Twenty three forms of human FGF have been defined, which can be divided into 7 subfamilies based on species and coding sequences (Table 1) [5]. FGF21 belongs to the hFGF subfamily (FGF19, FGF21, FGF23) whose isolated cDNA codes for a protein comprising 209 amino acids with a molecular weight of approximately 22.3 kDa and an amino acid sequence that is highly conserved in mammals. Although autocrine and paracrine, FGF21 is principally expressed in the liver [6]. Extra-hepatic tissues, such as white and brown adipose tissues [7], thymus [8], pancreatic beta cells [9], skeletal muscle [10], cardiac endothelial cells [11], and the hypothalamus [12] also express FGF21. The expression of FGF21 is under the control of PPAR-α (peroxisome proliferator-activated receptor-α) and PPAR-β [13] in different tissues. Due to the lack of specific binding sites associated with heparin, FGF21 is mainly released through endocrine-associated tissues and released into the blood, rather than being autocrine.

FGF21 was first isolated in 2000 when its outstanding ability to regulate glucose, lipid, and energy metabolism was confirmed, including improvement in insulin sensitivity, protection of islet beta cells, decreased plasma glucose levels, lowered triglyceride levels in the liver/serum, initiation of weight loss by improving energy consumption, and a reduction in the mass of fat [2]. Other members of the FGF family classically require an association with heparan sulfate proteoglycan (HSPG) for their physiological function to be available [14]. However, FGF19 is functional toward FGFR in the absence of heparin-like molecules, but there is a prerequisite for Klotho [15]. There are two forms of Klotho in humans. It is known that α-Klotho combines with FGF23 in the kidney, performing an important role in the metabolism of calcium and phosphate [16], whereas β-Klotho combines with FGF21 in the presence of FGFR to regulate carbohydrate and lipid metabolism [17] and with FGF19 to regulate the synthesis and secretion of bile acids [18]. Further studies have revealed the molecular mechanism of FGF21's role in humans—as an auxiliary receptor for β-Klotho which binds to the C-terminal and for FGFRs via the N-terminal, eventually forming a stable β-Klotho/FGFR complex that activates the downstream signal transduction pathway, resulting in protein generation through the FGF21/β-Klotho/FGFR pathway [19]. This research established that β-Klotho is an adaptor-like transmembrane molecule that binds directly to FGF21 to activate FGFRs, which serve as an activity-competent subunit. Furthermore, Yie has reported that the C-terminus of FGF21 is critical for binding to β-Klotho and the N-terminus critical for FGR activation [20].

However, it seems that not all tissues express β-Klotho. It has been found that β-Klotho expression is restricted to a relatively small number of tissues, such as adipose tissue, brain, liver, and pancreas, the consequence of which is tissue-selective binding to FGF21. Consistent with this, FGF21 initiates its action by activating FGFRs in the presence or absence of the co-factor β-Klotho, which has been found in liver and adipose tissues but not in skeletal muscle or heart tissues [20, 21]. FGFRs are known to have 4 genotypes—FGFR1, FGFR2, FGFR3, and FGFR4. FGF21 can bind with any of these four receptors, but their binding affinities are different. In the presence of β-Klotho, the affinity between FGF21 and the FGFR1-β-Klotho complex is significantly greater than that of FGFR4-β-Klotho [22–24]. Moreover, in different tissues, the strength of binding of FGF21 with its receptors is also different. For example, in adipose tissue, FGF21 performs its role through interaction with FGFR1 [25]. In the liver, binding occurs through the activation of FGFR2, thereby reducing cholesterol synthesis [26]. In the heart, FGF21-Klotho binds to FGFR1c and FGFR3 [22].

In recent years, there has been mounting evidence that increased levels of serum FGF21 are found in obese, insulin-resistant patients, and those with metabolic syndrome [27]. Thus, FGF21 is now thought to be a stress-response hormone in humans [28]. In addition, different types of physical stress, such as strenuous exercise [29], breastfeeding [30], diabetic nephropathy [31], cardiovascular [32], and other severe diseases [33, 34], also promote an increase in the concentration of circulating FGF21. Elevated serum FGF21 has been closely observed as a potential prognostic marker of polycystic ovary syndrome [35], mitochondrial disease [36, 37], pregnancy-

Table 1 Summary of the physiological functions of FGFs

Subfamily	Subtype	Tissue	Secretion pathway	Functions
FGF1 subfamily	FGF-1	Bain	Autocrine	Injury repair
	FGF-2	Adipose	Paracrine	Revascularization
				Neuronal development
				Glucose regulation
FGF2 subfamily	FGF-4	Embryo	Paracrine	Myocardial preservation
	FGF-5	Hair follicle		Muscle regeneration
	FGF-6	Heart		
FGF7 subfamily	FGF-3	Thyroid	Paracrine	Subtle
	FGF-7	Bone		Muscle regeneration
	FGF-10	Axoneure		Multiple organ development
	FGF-22			
FGF8 subfamily	FGF-8	Heart	Paracrine	Gastrulation development
	FGF-17	Pancreas		Cerebellar development
	FGF-18	Skeletal muscle		Skeletal development
				Lung development
				Tumorigenesis
FGF9 subfamily	FGF-9	Exist extensively	Paracrine	Lung development
	FGF-16			Heart development
	FGF-20			Vascular development
				Neurological function
				Tumorigenesis
iFGF subfamily	FGF-11	Bone	Autocrine	Neuromuscular function
	FGF-12	Heart		Neurological function
	FGF-13			
	FGF-14			
hFGF subfamily	FGF-19	Liver	Autocrine	Heart development
	FGF-21	Adipose		Energy metabolism
	FGF-23	Thymus		Phosphate metabolism
		Heart		Vitamin D metabolism
		Skeletal muscle		Bile acid metabolism

induced hypertension [38], and Cushing's syndrome [39] (Table 2). It has been suggested that increasing production of FGF21 in the early stages of disease is a compensatory response of the organism [47]. However, some researchers have suggested that an early increase in serum FGF21 as a disease develops contributes to the development of FGF21 resistance, which is involved in the pathogenesis of other related diseases. By analyzing these related diseases of metabolic disorders, it has been observed that other indicators are also significantly elevated, such as TG (triglyceride), FFA (free fatty acid), HDL-c (high-density lipoprotein-c), LDL-c (low-density lipoprotein-c), body mass index (BMI), and waist circumference [48]. These indicators are closely related to obesity. The potential mechanism may be that FFAs (free fatty acids) and agonists for PPAR-α stimulate its activation in the liver, inducing an increase in circulating levels of FGF21. In fact, under normal physiological conditions, FGF21 can maintain normal levels of chylous particles and VLDL by removing excess lipid from the body. Therefore, it is reasonable to speculate that combining serum FGF21 levels with other related blood lipid metabolic parameters as an early diagnostic indicator of disease is a novel direction for prevention and diagnosis of metabolic diseases. Because measuring FGF21 levels is simple and convenient, it is not an invasive procedure. Therefore, a test for FGF21 may be useful for patients who require screening for a relevant metabolic disorder or those at high risk of those diseases.

Unlike conventional insulin therapy, treatment with FGF21 does not cause the side effects that do traditional antidiabetic drugs, such as hypoglycemia and edema, among others [49]. A possible explanation is that FGF21 performs a physiological role in health and exerts pharmacological effects in a host that is healthy. However, due to the lack of mitotic function, elevated FGF21 levels do not cause carcinogenic events, thereby reducing the risk from clinical medication [21]. Therefore, based on the above-mentioned characteristics and benefits, FGF21 is expected to become a novel choice for clinical treatments of metabolic diseases.

Table 2 Summary of major pharmacological studies of elevated serum FGF21in four types of circumstances

Circumstances	Conditions	Cytokines	References
Physical stress	Strenuous exercise	CIEDA, KLB	[29]
	Breastfeeding	TPO	[30]
	Diabetic nephropathy	Nrf2, SREBP1c	[31]
	Cardiovascular diseases	ERK1/2, AMPK, PI3K	[32, 40–42]
	Severe diseases	PPAR-α, pERK	[33, 34]
Pathological stress	Polycystic ovary syndrome	?	[35]
	Pregnancy-induced hypertension	PPAR-α, PPARγ, KLB	[38]
	Cushing's syndrome	?	[39]
Mitochondrial diseases	N/A	Drp-1, eIF2-α, Sirt-1	[36, 37, 43]
Oxidative stress	N/A	NF-κB, Nrf2	[44–46]

A role for FGF21 in the development of diabetic cardiomyopathy

Diabetes is an absolute or relative insufficiency of insulin, characterized by hyperglycemia and hyperlipidemia. In recent years, the incidence of diabetes has increased year on year, with cardiovascular complications secondary to diabetes becoming the leading cause of death in diabetic patients. Among them, diabetic cardiomyopathy (DCM) is a major heart complication of diabetes, with high morbidity and high risk, closely related to the high incidence of cardiovascular disease and high mortality in diabetic patients [50]. Studies confirm that insulin resistance [51], left ventricular hypertrophy [52], increased rate of apoptosis in cardiomyocytes [53], myocardial fibrosis and remodeling of myofibrils [54], cardiac autonomic neuropathy, calcium ion overload in myocardial cells, microvascular lesions, oxidative stress, modifications to extracellular matrix, and metabolic abnormalities are important factors that promote DCM and facilitate its progression [55, 56]. In 1972, Rubler and others proposed the concept of diabetic cardiomyopathy for the first time following further pathological studies [57]. Diabetic cardiomyopathy encompasses a broad range of focal myocardial necrotic injuries caused by a combination of diabetes mellitus, cardiac microvascular lesions, and myocardial metabolic disorders. Early diastolic dysfunction usually manifests as decreased myocardial compliance and obstructions to diastolic filling. Late systolic dysfunction is the most common, with patients prone to suffering congestive heart failure [58]. It has been recognized that diabetic cardiomyopathy is an independent primary disease, its onset independent of hypertension, coronary artery disease, or other known heart diseases [59]. It is attributed to the complex pathogenesis of diabetic cardiomyopathy, usually diagnosed in the late stages; so, no effective treatment specifically for DCM has yet been defined.

As is well-known, hyperglycemia initiates diabetic cardiomyopathy and contributes to various pathological processes of diabetic cardiomyopathy. FGF21 is an important metabolic regulator with key roles in the regulation of various fundamental physiological and metabolic processes, such as reducing plasma glucose levels and lowering levels of triglyceride in the liver and serum. Recent clinical and subclinical studies have found that increased serum FGF21 is closely associated with diabetic cardiomyopathy [60], and, so, it is considered a potential biomarker. However, whether increased serum FGF21 is the basis of DCM pathogenesis or a key molecule involved in repairing damage from DCM is still unclear. Increasing evidence that injection of exogenous FGF21 mostly has a protective effect on cardiovascular disease suggests that FGF21 is not only a marker of cardiovascular risk index but also has protective effects on the cardiovascular system, which help in reducing cardiovascular disease, including DCM. Thus, there is little doubt that FGF21 has a protective role in the pathogenesis of diabetic cardiomyopathy. Following numerous in-depth studies, an understanding of the pathological mechanisms and processes of diabetic cardiomyopathy suggests that traditional treatments, such as anti-diabetic drugs and those that improve heart function, cannot fundamentally improve the clinical symptoms or cure diabetic cardiomyopathy; so, novel treatment paradigms are urgently required [61–63]. Attention should therefore focus on the identification of appropriate drugs and targets. Drugs such as FGF21 can inhibit the development of diabetic cardiomyopathy in many respects. This article attempts to clarify the potential relationship between FGF21 and major pathological processes of diabetic cardiomyopathy, including oxidative stress, inflammatory response, myocardial cell energy metabolism, and apoptosis, in order to reveal possible therapeutic targets and define potential areas of research.

Review

Protective effects of FGF21 in anti-apoptosis pathways

It is known that diabetic cardiomyopathy (DCM) is a specific cardiac complication, a chronic pathological modification of

cardiac muscle in response to the acute reactions caused by diabetes [64]. A key early cardiac response in diabetic cardiomyopathy is apoptosis [53]. Several studies have found that caspase-3 activity, DNA fragmentation, and TUNEL-positive apoptotic cells increase in STZ-induced diabetic rats compared with wild-type (WT) animals, accompanied by diastolic and contractile dysfunction. It has been confirmed that myocardial apoptosis occurs in DCM lesions, combined with decreased cardiac function [65]. In particular, endoplasmic reticulum (ER) has been the most studied cellular element proposed as a mechanism for myocardial cell apoptosis in diabetic patients, fulfilling multiple cellular functions, including regulation of protein synthesis and post-synthesis folding, governing the response to cellular stress, regulation of calcium transport in cells in addition to being the organelle in which cholesterol, steroids, and lipids are synthesized [66]. Variations in the cellular environment caused by ischemia, hypoxia, heart shock, gene mutations, and elevated protein synthesis can impact ER function which results in ER stress, leading to further cardiomyocyte (CM) apoptosis [67]. It has been established that UPR (unfolded protein response) is the initial step in ER stress, activated by a series of external factors. UPR affects intracellular translation and transcription with ER stress being alleviated through the following three signaling pathways: pERK (protein kinase R-like ER kinase), IRE-1 (inositol-requiring protein-1), and ATF-6 (activating transcription factor-6) [68–70]. The pERK signaling pathway immediately restricts intracellular protein translation, while IRE-1 and ATF-6 signals promote the folding of misfolded proteins and degradation of unfolded proteins through upregulation of molecular chaperone genes of the endoplasmic reticulum.

A previous study revealed that ER stress might be involved in the development of DCM in diabetic heart tissue, in which markedly increased expression of FGF-21 was observed in an STZ-induced type 1 diabetic rat model [40]. In addition, we have found that FGF21 is the target gene for ATF4 and CHOP, with transcription and mRNA stabilization responsible for ATF4 and CHOP-mediated induction of FGF21 expression in ER stress [71]. In FGF21-knockout (KO) mice, ER stress was significantly elevated with the rate of cell apoptosis increased. This provides a theoretical basis for FGF to improve the symptoms of diabetes by inhibiting stress in endoplasmic reticulum of myocardial cells in diabetic patients. Liang et al. reported that overexpression of FGF-21 in H9c2 cells significantly decreased levels of related proteins via the PERK pathway [43]. Thus, FGF21 reduces cardiomyocyte apoptosis induced by ER stress in DCM through inhibition of the pERK-eIF2a-ATF4-CHOP pathway in ER stress. Interestingly, we also detected apoptosis mediated by JNK protein expression and found that, compared with the control group, expression levels of the pro-apoptotic proteins p-JNK, GRP78, c-caspase-3, and Bax/Bcl-2 were induced in the TM (tunicamycin) and pcDNA4 + TM group animals, with levels that were significantly greater ($P < 0.05$–0.01). Those expression levels were significantly lowered ($P < 0.05$–0.01) following treatment with pcDNA4-FGF21 + TM, suggesting that FGF21 can reduce myocardial apoptosis by regulating that process as mediated by the JNK pathway [72, 73]. Recently, Ming revealed that the FGF21-β-Klotho-FGFR1 signaling axis plays a role against ER stress through regulation of the majority of ER stress-response genes, including Atf6, CHOP, Grp78, Ip3r1, and Ire1a, which provides a basis for further study of the underlying mechanisms [74]. Thus, in summary, through animal experiments, it has been found that FGF21 reduces apoptosis in myocardial cells induced by ER stress through various signaling pathways.

AMP-activated protein kinase (AMPK), highly conserved in eukaryotic cells, is a serine-threonine protein kinase which can sense the ratio of AMP to ATP [75, 76]. When both rise, they activate AMPK and subsequently the down-stream proteins. AMPK, on one hand, promotes the production of ATP, while on the other inhibits the metabolic synthesis associated with the consumption of ATP. When an individual suffers from diabetes, hyperlipidemia, or other metabolic syndrome, the activity of AMPK is dramatically reduced, with a concomitant reduction in the synthesis of ATP by mitochondria causing an energy metabolic disorder, leading to cardiac dysfunction [77, 78]. Recently, we found that FGF21 protects against cardiac apoptosis in a type 1 diabetic mouse model by activating the ERK1/2-P38MAPK-AMPK pathway [41] with pharmaceutical inhibition of AMPK leading to a significant decrease in FGF21-induced cardio-protection and restoration of cardiac function in response to global ischemia [42]. Other studies have demonstrated that FGF21 suppresses DCM through multiple signaling pathways (Fig. 1). As a classical cytokine, FGF21 functions as a regulator by binding to its receptor FGFR1c in the presence of β-Klotho. Growing numbers of studies demonstrate that FGF21 provides beneficial effects against DCM possibly due to inhibition of cardiac apoptosis. For example, FGF21 prevents stress-induced apoptosis of myocardial cells via a decrease in the production of reactive oxygen species (ROS) by the FGF21/PPAR/Sirt1 signaling pathway. FGF21 also prevents diabetic cardiomyopathy via the ERK1/2-CREB-PGC-1α signaling pathway which regulates lipid metabolism and cell survival. Taken together, these results suggest that FGF21 therapy could play a protective role in the anti-apoptosis pathways of myocardial cells.

Anti-inflammatory mediator pathway

Nuclear factor κB (NF-κB) is a nuclear transcription factor that exists in numerous cell types and can regulate the expression of a large number of genes, thereby mediating an inflammatory response [79]. It has been shown that NF-κB can induce the expression of inflammatory factors, such as IL-1,

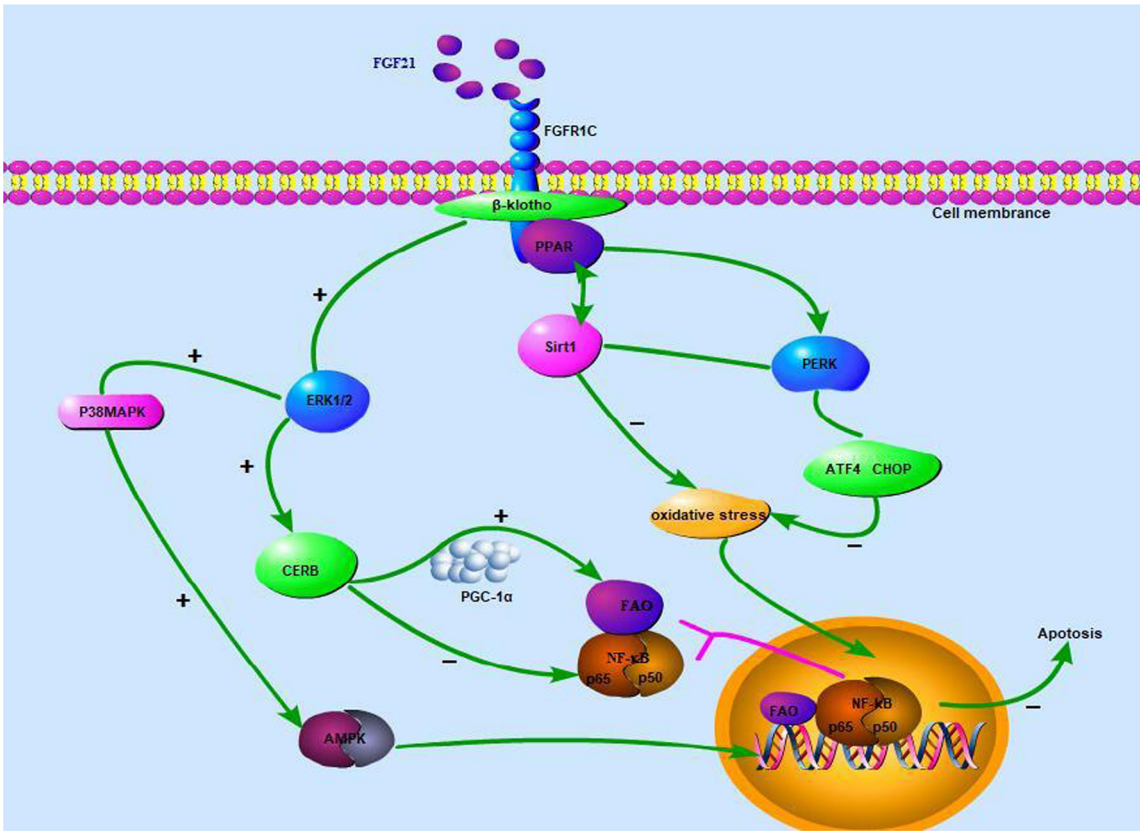

Fig. 1 The primary mechanisms through which FGF21 has protective effects on myocardial cell injury. PPAR, peroxisome proliferator-activated receptor; ERK, extracellular-regulated protein kinase; MAPK, mitogen-activated protein kinase; AMPK, adenosine 5′-monophosphate (AMP)-activated kinase; CREB, cAMP-response element-binding protein; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PERK, protein kinase R-like ER kinase; ATF4, activating transcription factor-4; CHOP, C/EBP-homologous protein; Sirt1, silent information regulator-1

TNF, and IFN. According to the findings of a previous study, activation of NF-κB is thought to constitute a part of the stress response as it is activated by a variety of stimuli, including growth factors, cytokines, lymphokines, UV light, pharmacological agents, and stress [80]. Activation of the NF-κB signaling pathway correlates closely with the incidence of diabetic cardiovascular disease and is an important intermediate link in the pathogenesis of diabetic vascular complications. Hyperglycemia and impaired protein utilization lead to the overproduction of AGEs (advanced glycation end products) in diabetic patients which then bind to specific receptors in cell membranes known as RAGEs (receptor for advanced glycation end products). These promote the release of ROS and translocation of NF-κB into the nucleus. Activation of NF-κB causes transcription of related inflammatory factors, ultimately leading to vascular endothelial cell injury and smooth muscle cell proliferation that induce DCM. Li et al. demonstrated that, compared with a normal mouse group, expression of NF-κB mRNA increased significantly in the diabetic cardiomyopathy group, which then controlled the expression of a series of genes downstream, including ICAM-1 (intercellular cell adhesion molecule-1), TNF-α, IL-1β, and COX-2, which contribute to the development of a local inflammatory response [81]. Treatment with an extrinsic source of FGF21 caused significant upregulation of AKT phosphorylation in WT mice with type 1 diabetes mellitus (induced by streptozocin), a result similar to that obtained with phosphorylation levels of the downstream signaling molecule GSK-3β [44]. Furthermore, Xu and Zhang reported that FGF-21 treatment inhibited the activation of HSCs (hematopoietic stem cells) via downregulation of TGF-β expression, NF-κB nuclear translocation and the phosphorylation levels of smad2/3 and IκB-α ($P < 0.05$) [45]. Thus, the NF-κB pathway performs an important role in the pathogenesis of DCM and FGF-21 by alleviating the inflammatory response induced by diabetes and so reduces the development of diabetic cardiomyopathy.

Akt is a serine-threonine protein kinase that is activated by various extracellular stimuli through a phosphatidylinositol 3-kinase (PI3-kinase) pathway. A large number of studies have implicated Akt signaling in inflammatory pathways in addition to being the regulator of cellular growth, organ size, and cellular hypertrophy [82, 83]. Downregulation of p-Akt during the early and mid stages of diabetes limits Akt-induced

utilization of glycogen, with local inflammation causing cognitive impairment and oxidative stress [84, 85]. Moreover, the Akt pathway is related to transcription of the genes for IL-1β, IL-6, and TNF-α. Shen et al. reported that activation of Akt down-stream proteins caused a considerable increase in DCM in mice, while phosphorylation of Akt proteins decreased significantly compared with the control group. Another study demonstrated that the expression of FGF21 and AKt in the skeletal muscle is closely related. FGF21 expression levels that were significantly increased in serum and skeletal muscle of Akt1 transgenic mice were regulated by the PI3/Akt signaling pathway [44]. In mice with diabetic cardiomyopathy induced by STZ, FGF-21 increased cardiac function and decreased mRNA levels of IL-1β, IL-6, TNF-α, and TNF-β, which may be associated with increased phosphorylation of Akt [86]. These results suggest that Akt mediates the inhibitory effect of FGF in cardiac inflammatory cytokines induced by diabetic cardiomyopathy.

It is known that lipopolysaccharide (LPS) performs an important role in the inflammatory response of cardiomyocytes, which significantly increases the expression of pro-inflammatory genes. Thus, the effects of FGF21 on cardiac cell response to LPS were studied. Results demonstrated that compared with WT mice, the mRNA levels and plasma protein levels of pro-inflammatory factors, such as IL-6 and MCP-1, were greatly increased in FGF21-knockout mice [87]. Surprisingly, we found that the inhibitory effects of FGF21 on myocardial inflammation were closely related to the induction of PCG-1α. A rational explanation for this may be that FGF21 performs an anti-inflammatory role through the NF-κB/PCG-1α pathway, but further clinical studies are urgently required to establish whether FGF21 can be used as a novel treatment tool to improve myocardial inflammatory response.

FGF21 and oxidative stress pathway

Oxidative stress is defined as an imbalance between pro-oxidant and anti-oxidant factors in favor of the former. Pro-oxidants, such as ROS, are essential for the normal function and activity of cell signaling molecules [88]. Under physiological conditions, due to the body's energy metabolism, ROS, such as superoxide radicals, hydroxyl radicals (OH^-), and hydrogen peroxide (H_2O_2), are continuously produced in many cells. However, ROS levels are controlled by numerous regulatory enzymes, such as superoxide dismutase, glutathione peroxidase, catalase, and thioredoxin; so, concentrations of ROS are in dynamic balance. When the production of ROS becomes excessive, oxidative stress develops and initially causes a harmful effect on the functional integrity of biological tissue [89, 90]. As a result of the accumulated level of ROS, these highly reactive molecules can induce irreversible damage to the cell, including direct oxidation of DNA, proteins, and lipid, in addition to activation of stress-sensitive pathways leading to cell damage [91]. It has been postulated that hyperglycemia, a key clinical manifestation of diabetes, may produce ROS through the formation of AGEs and modified polyol pathway activity and, also, through the activation of NADPH oxidase via protein kinase C (PKC) [92, 93]. Furthermore, in high-glucose and high-lipid environments, increased oxidative stress directly damages pancreatic islet β cells and reduces their content of antioxidant enzymes, which is sensitive to oxidative damage [94]. In addition, oxidative stress inhibits insulin expression and secretion through insulin signaling pathways. The end result is a decrease in insulin secretion [95]. Thus, oxidative stress induced by excessive concentrations of ROS performs a key role in the pathogenesis of heart failure in diabetic patients, causing extensive focal necrosis, apoptosis, and fibrosis in the myocardium, which causes systolic-diastolic dysfunction.

In recent years, studies have found that oxidative stress is also important in the initiation and development of diabetes and its complications, especially diabetic cardiomyopathy [96] (Fig. 1). An increase in mitochondrial oxidative stress is the central factor in diabetes tissue injury. Hyperglycemia and insulin resistance increase glucose and fatty acid oxidation causing oxidative stress and resulting in massive accumulation of ROS in mitochondria. Indeed, impaired antioxidant defense in diabetes itself further enhances the extent of oxidative stress [97]. Nrf2 is an important transcription factor that regulates the cellular antioxidant stress response, which upregulates the expression of antioxidant enzymes, increases cell resistance to oxidative stress, and removes oxygen free radicals. Many studies have demonstrated that the Nrf2/ARE signaling pathway is key to oxidative stress in cells [98]. Antioxidant enzymes downstream of the ARE pathway in the Nrf2 compartment include CAT, SOD, and GSH-px. As reported by Wu, the expression of GSH in the liver of diabetic mice was significantly lower than that of control mice, and the levels of ROS significantly greater, suggesting that increased oxidative stress leads to apoptosis in hepatocytes [46]. Further studies demonstrated that administration of FGF21 in diabetic mice led to a significant decrease in the levels of ROS, while n-Nrf2 increased significantly, c-Nrf2 was dramatically reduced, and so Nrf2 activity was restored and myocardial antioxidant activity enhanced. Unexpectedly, application of extrinsic FGF21 resulted in the expression of GSH to be not significantly changed in diabetic mice, suggesting that the antioxidant effect caused by treatment with FGF21 was not achieved due to the antioxidant GSH but partly by Nfr2.

As described previously, mitochondria perform a pivotal role in apoptosis, with the mitochondrial oxidative stress pathway being the principal mechanism leading to the apoptosis of cardiomyocytes [99]. Bax and Bcl-2 are two key members of the Bcl family. Bax, which senses cell damage or stimulation, is commonly found in the cytoplasm. Following damage to or

stimulation of a cell, Bax relocates to the surface of mitochondria and destroys the function of the anti-apoptotic protein Bcl in its normal state. In addition, Bax forms a pore that spans the mitochondrial outer membrane, leading to a drop in membrane potential, efflux of cytochrome C and apoptosis-inducing factors, and activation of caspase-9. Bcl-2 is an important intracellular component that inhibits cell apoptosis by associating with the mitochondrial outer membrane, stabilizing its permeability, and so protecting the integrity of the mitochondrion [100–102]. Both proteins play an important regulatory role in the mitochondrial apoptotic pathway [103]. Results of a study using RT-PCR has shown that, compared with a blank control, the expression of Bcl mRNA in mice in the H_2O_2 treatment group decreased significantly, whereas the expression of Bax mRNA increased significantly, with the rate of apoptosis increasing significantly [104]. Further studies demonstrated that the number of apoptotic H9c2 cells induced by H_2O_2 reduced significantly after treatment with FGF21. Quantification of intracellular ROS concentration and lipid oxidation demonstrated that FGF21 protected myocardial cells against oxidative damage accompanied by a reduction in ROS and MDA (malonaldehyde) levels in H9c2 cells, suggesting that FGF-21 may protect cardiomyocytes by regulating the mitochondrial redox system and reducing excessive accumulation of ROS induced by H_2O_2 [105].

These results suggest that exogenous FGF21 protects from heart injury in DCM through antagonizing oxidative stress, but the quantity of FGF21 injected in these studies was considerably greater than that in normal physiological conditions [106]. Recently, we demonstrated that the heart is a target in addition to being a source of FGF21 [11]. Expression of FGF21 in the heart is under the control of the protein deacetylase Sirt1 (sirtuin1). In a high-sugar, high-fat environment, activation of the Sirt1 pathway induced cardiac secretion of FGF21, which acted in an autocrine manner to prevent oxidative stress in cardiomyocytes through promotion of the expression of certain antioxidant genes (e.g., Ucp2, Ucp3, or Sod2) [67]. To summarize, FGF-21 performs a role in suppressing apoptosis in myocardial cells induced by oxidative damage both in vitro and in vivo, protection occurring through regulation of apoptosis-related genes and the oxidoreductase system. This is important for FGF-21 antioxidant research and the prevention and treatment of cardiovascular and other diseases caused by oxidative stress injury. However, this evidence was gathered in animals with a lack of research data from clinical studies and so clearly requires further investigation.

FGF21 promotes fatty acid oxidation in myocardial cells

Lipid accumulation in the heart plays a causative role in the development of DCM. In patients with diabetic cardiomyopathy, the activity of GLUT4 declines due to the high sugar and fat within the tissue environment [107]. Thus, utilization of glucose cannot meet myocardial cell demand, and so mitochondrial fatty acid oxidation (FAO) is elevated to meet that energy demand, inevitably causing a greater quantity of oxygen free radicals due to fatty acid β-oxidation. One study found that cardiomyocyte mitochondrial dysfunction and the level of fatty acid β-oxidation decline in patients with diabetic cardiomyopathy, leading to lipid deposition in myocardial cells in great quantities which promotes the development of the pathological processes related to diabetic cardiomyopathy. However, it has been found that deletion of FGF21 in mice exacerbates this pathological process by increasing cardiac lipid accumulation, although the mechanism by which this occurs is currently unclear [108]. Conversely, Yan reported that both FGF21-KO and WT diabetic mice typically had diabetic hyperlipidemia, with no significant difference observed in plasma triglyceride levels between the two strains [108]. However, when exogenous FGF21 was injected, lower quantities of lipid were deposited in the myocardial cells in diabetic mice which delayed the symptoms of diabetic cardiomyopathy, confirming that FGF21 can delay the effect of diabetes by inhibiting cardiomyocyte lipid oxidation. This specific molecular mechanism requires further study. Moreover, due to the FFA disorder in diabetic patients, cardiac myocytes respond to this phenomenon by upregulating the expression of enzymes required for mitochondrial β-oxidation. These enzymes are under transcriptional control of the nuclear transcriptional factor PPAR. We found that high concentrations of FFA activate PPAR, leading to increased FFA consumption through myocardial fatty acid oxidation and utilization. PGC-1α is a transcriptional co-activator involved in the control of energy metabolism and oxidative stress in several tissues, including the heart. It was previously reported that cardiac expression of PGC-1α is repressed by hypertrophic and pro-inflammatory stimuli. It has recently been found that the expression of PGC-1α is significantly lower in STZ-induced type 1 diabetic mice that are FGF21 gene knockout, and that, accordingly, the level of FAO was observed to diminish, the mice becoming prone to myocardial cell lipid deposition, leading to further cardiac dysfunction [109]. However, in the transgenic mice, over-expression of FGF21 increased the level of PGC-1α significantly and increased the degree of FAO. This indicates that FGF21 can increase myocardial cell FAO through the FGF21/PGC-1a conduction pathway, which provides an internal mechanism for improving myocardial function through FGF21. In addition, it is known that FGF21 can enhance GLUT1 activity and improve glucose utilization in the cardiac myocardium, which removes the energy supply barrier in diabetic myocardial cells. However, one limitation of the study under discussion is the lack of correlation with type 2 diabetes. It is widely believed that DCM in type 1 and type 2 diabetes has a similar pathological mechanism [110],

but FGF21 has proven to exhibit different serum levels in type 2 diabetes compared with that of type 1 [111]. In order to ensure greater clinical relevance of FGF21 and ascertain whether it performs a similar role in the development of both types of diabetes, comparative studies that test this proposition are required in the future.

CD36 appears to perform a key role in mediating heart metabolism in diabetic animals [61, 112]. Small-molecule inhibitors of CD36 have recently been developed which can prevent any FA that has been taken up from combining with CD36, to further reduce cardiac lipid accumulation [113]. Not only do these CD36 inhibitors perform a protective effect in diabetic cardiomyopathy, it has also been found that they are effective in eliminating excessive FA accumulation in the heart in addition to preventing heart failure. Under physiological conditions, increased cardiac CD36 expression can compensate for the decreased supply of long-chain fatty acids [114]. For a diabetic, elevated cardiac CD36 expression mediates excessive uptake of FA leading to cardiac lipid accumulation [115]. In FGF21-KO mice, cardiac CD36 expression has been shown to become further upregulated, concomitant in a time-dependent manner with excess cardiac lipid accumulation. In addition, cardiac AMPK phosphorylation, an indicator of energy homoeostasis, was observed to further decrease in FGF21-KO diabetic mice, also in a time-dependent manner [108]. As mentioned previously, PGC-1α, a critical regulator of fatty acid β-oxidation and a key mediator of FGF21 regulation of lipid metabolism, decreased significantly but only in the hearts of FGF21-KO diabetic mice during the later stages of DCM. It has been reported that high doses of exogenous FGF21 can reverse those reductions. The results of FGF21 deletion-aggravated DCM studies indicate that FGF21 may be a therapeutic target for the treatment of diabetic cardiovascular complications, including diabetic cardiomyopathy.

Conclusions

Diabetes mellitus (DM) is among the world's most common metabolic disorder. The number of global diabetic patients rose to 415 million in 2015, approximately 8.3% of the adult population. From 2012 to 2015, DM and its complications were estimated to cause 1.5 to 5.0 million deaths each year [116]. Cardiac dysfunction, namely diabetic cardiomyopathy (DCM), is a major complication that accounts for more than half of diabetes-related morbidity and mortality [117–119]. The search for agents that are effective against diabetic cardiomyopathy is urgent as DCM is a problem that requires a solution. FGF21, a recently discovered endogenous secretory hormone, plays an important role in glycolipid metabolism.

In this review, we have retrospectively analyzed the protective effects of FGF21 in the pathological process of diabetic cardiomyopathy. As numerous studies have shown, FGF21 performs an inhibitory role in myocardial apoptosis in diabetic cardiomyopathy through a variety of signaling pathways in addition to expressing related proteins, thus reducing the pathological processes in diabetic cardiomyopathy. It is known that Akt and NF-κB are major proteins involved in the inflammatory response in diabetic cardiomyopathy. FGF21 can alleviate the inflammatory response induced by diabetes by regulating the NF-κB signaling pathway to suppress the development of diabetic cardiomyopathy. As observed with the PI3/Akt signaling pathway, FGF21 performs a protective role in the inflammatory response in diabetic cardiomyopathy. Oxidative stress is a part of the whole pathological process in DCM, which contributes to myocardial apoptosis, cardiac fibrosis, hypertrophy of myocardium, and myocardial calcium overload. High doses of exogenous FGF21 perform an excellent role in reducing oxidative stress in myocardial cells both in vitro and in vivo, hence demonstrating the potential FGF21 has as a treatment for DCM. We also analyzed the causes of abnormal lipid metabolism and lipid damage to myocardial cells. Further studies found that the specific mechanism and signaling pathways related to FGF21 improve lipid metabolism in diabetic mice. Although there are many studies of FGF21 as a treatment for DCM, they are not sufficiently rigorous to utilize as a definitive therapy for DCM.

It is known that serum levels of FGF21 are significantly increased in the early stages of the pathogenesis of various metabolic diseases, but they become significantly reduced in the later stages. It can be speculated that the increase in early levels of FGF21 is compensation by the host as a reaction to the metabolic disease. However, it has been proposed that elevation of FGF21 levels actually contributes to the pathogenesis of the disease, and, so the concept of FGF21 resistance was hypothesized. During the pathological process of diabetic cardiomyopathy, it has been verified that FGF21 treatment functions to reduce DCM, but the specific mechanisms are still controversial. For example, exogenous FGF21 significantly inhibits hypertrophy in cardiomyocytes in diabetic mice, but it has been confirmed experimentally that early high serum levels of FGF21 in diabetic animals participate in the induction of myocardial hypertrophy, which appears to be a contradiction. At present, the majority of experiments are performed in type 1 diabetic mice, with the necessity of effectively demonstrating the mechanisms of action of FGF21 in mice with type 2 diabetes having been ignored. It remains to be explored whether the dose of FGF21 as a treatment for DCM is too high compared with physiological concentrations. Therefore, use of FGF21 for the treatment of metabolic diseases, especially DCM, has been partially confirmed, but, for clinical treatment of disease, further research is required.

Contributions of authors XZ reviewed the literature, researched the data, and drafted the manuscript. LY, YH, XX, FT, and PY contributed to the discussion and reviewed the manuscript. YH and BQ are the guarantors of this work. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not describe any studies with human participants performed by any of the authors.

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