VIA MEDICA
REVIEW ARTICLE
ISSN 2450–7458
e-ISSN 2450–8187

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A Comprehensive Review on the Metabolic Cooperation Role of Nuclear Factor E2-Related Factor 2 and Fibroblast Growth Factor 21 against Homeostasis Changes in Diabetes

ABSTRACT

Objective: Type 1 and type 2 diabetes are associated with metabolic disorders including hyperglycemia, hyperlipidemia, and inflammation, leading to the production of reactive oxygen species and nitrogen activators. In these cases, some of the body's innate factors are activated to cope with these dangerous situations. The purpose of the review is to explain the collaboration between the nuclear factor E2-related factor 2 (NRF2) and fibroblast growth factor 21 (FGF21) in homeostasis and body metabolism with a focus on diabetes.

Materials and methods: This review is based on searching the PubMed database, SCOPUS, Elsevier and citation lists of relevant publications. Subject heading and key words used include diabetes, oxidative stress, inflammation, NRF2, and FGF21. Only articles in English were included.

Results: NRF2 and FGF21 are two attractive biomarkers for the diagnosis of specific metabolic disorders and therapeutic targets, which have been implicated as therapeutic targets for the management of diabetic complications. The combination of both factors leads to the regulation of antioxidant and anti-inflammatory responses and metabolic pathways.

Conclusions: Given most studies of NRF2- and FGF21--based therapeutic interventions in animal models and the possibility of not achieving the same results in humans, further clinical studies are needed to determine the efficacy of NRF2 and FGF21 in treatment of patients with diabetes. (Clin Diabetol 2022; 11; 6: 409–419)

Keywords: fibroblast growth factor 21, nuclear factor E2-related factor 2, elements of the antioxidant response, diabetes

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Clin Diabetol 2022, 11; 6: 409–419
DOI: 10.5603/DK.a2022.0051
Received: 8.03.2022 Accepted: 20.09.2022

Introduction

Diabetes remains one of the most important healthcare challenges in the world. Both types of disease are of genetic and environmental origin, with metabolic abnormalities including hyperglycemia, hyperlipidemia, and inflammation, which lead to the production of reactive oxygen species (ROS) and reactive nitrogen species (NOS). Homeostasis refers to the body's natural response to abnormal changes in order

to maintain normal conditions. In chronic diseases such as diabetes, changes in the homeostasis activate factors to prevent adverse and pathological conditions. Studies have shown that the main cause of diabetes complications, including micro- and macrovascular complications of nephropathy, retinopathy and cardiomyopathy, among other complications, is due to oxidative stress caused by the high production of these compounds. In such cases, some of the body's innate factors such as nuclear factor E2-related factor 2 (NRF2) are activated to deal with such a dangerous situation. NRF2 is a transcription factor that increases in response to oxidative stress [1, 2]. In addition to its antioxidant protective effect, it participates in various biological processes and is involved in homeostasis by regulating some genes involved in metabolism, proteostasis, mitochondrial physiology, tissue regeneration, inflammation, autophagy and immune processes [2]. Fibroblast growth factor 21 (FGF21) which is transcriptionally regulated by PPARα, is induced through increase in plasma free fatty acid and involves in glucose and lipid metabolism. It improves insulin resistance, hyperglycemia and dyslipidemia through various mechanisms [3, 4]. FGF21 can reduce inflammation, cell death, and organ damage through the up-regulation of NRF2.

Both NRF2 and FGF21 are factors that underlie changes in the level of gene expression and consequent changes in cell signaling in diabetes and are inversely related to oxidative stress, the main destructive factor of diabetes. Therefore, considering the potential of both factors to be proposed as medical and therapeutic targets, more research is needed in this respect at the clinical level and related cell lines. In this review, we investigate the role of NRF2 and FGF21 and related mechanisms against homeostasis changes in diabetes.

Materials and methods

Scopus and Web of Science were good databases to start with for our research topics. Subject heading and key words used included diabetes, oxidative stress, inflammation, NRF2, and FGF21. The search words consisted of both MeSH heading words and free text words. Then, we focused our search with specific databases including PubMed, SCOPUS, Elsevier and citation lists of relevant publications. After that, a selective search was performed among the uploaded articles to exclude studies not related to our topics and also to obtain the outputs of the selected studies. Although we tried to focus on studies from 12 years ago, we came across older studies whose results are still cited in new papers, and are also referenced in this review. All the authors of the article were involved in searching for articles and choosing the topic. The search was limited to articles written in English.

NRF2, an anti-stress transcription factor

Nuclear factor erythroid 2-related factor 2 (NRF2) is an essential transcription factor that is activated in response to oxidative stress and plays an essential role in cell protection and survival. NRF2 encoded by the *NFE2L2* gene is a leucine zipper (bZIP) protein with seven NRF2-ECH homology (Neh) domains (Neh-1 to Neh-7) (Fig. 1) and induces many cytoprotective genes by binding to the antioxidant response element (ARE) in promoter regions. It is expressed in most eukaryotic cells and in all human tissues, especially those involved in xenobiotic metabolism, including kidney, liver, and adipose tissue [5]. Studies over the past decade have proven its role in protecting against oxidative stress via regulating the expression of antioxidant proteins [6–8]. In addition to antioxidant protective effect, it participates in various biological processes and plays a pleiotropic role in homeostasis by regulating some genes involved in metabolism, proteostasis, mitochondrial physiology, tissue remodeling, inflammation, autophagy, and immune processes [9, 10].

Under normal physiological conditions, the half-life of NRF2 is only 20 minutes [11]. NRF2 is tightly kept by a cluster of cytosolic proteins that degrade it quickly. Kelch-like ECH-associated protein 1 (Keap1), as a repressor protein, traps NRF2 in the cytoplasm and facilitates its ubiquitination which occurred by Cullin 3, leading to subsequent proteolysis by the 26S proteasome. Keap1 is a cysteine-rich protein that can be modified by different oxidant compounds or electrophilic stress. Oxidative stress, disrupts the Keap1-Cul3 ubiquitination system by oxidation of the critical cysteine residues in Keap1 specially Cys-151, Cys-273, and Cys-278 [12]. Oxidized cysteine residues of Keap1 destabilize the Keap1-NRF2 complex, causing NRF2 to dissociate and escape from ubiquitination. The free NRF2 is phosphorylated at Ser-40, then transported to the nucleus, where it binds to one of the small Maf proteins, including MafF, MafG, and MafK, or Jun protein to form a heterodimer [10, 13]. The heterodimer binds to the ARE area in the upstream promoter region of EpRE/ARE-response genes, and induces their transcription [14]. The Keap1-independent β-TrCP mechanism is another pathway for NRF2 degradation that can detect phosphorylated NRF2 and facilitate its ubiquitination [15]. Other mechanism of NRF2 regulation in response to inducing signals is acetylation/deacetylation that affects the transcription activation, nuclear translocation, and degradation of NRF2 [16].

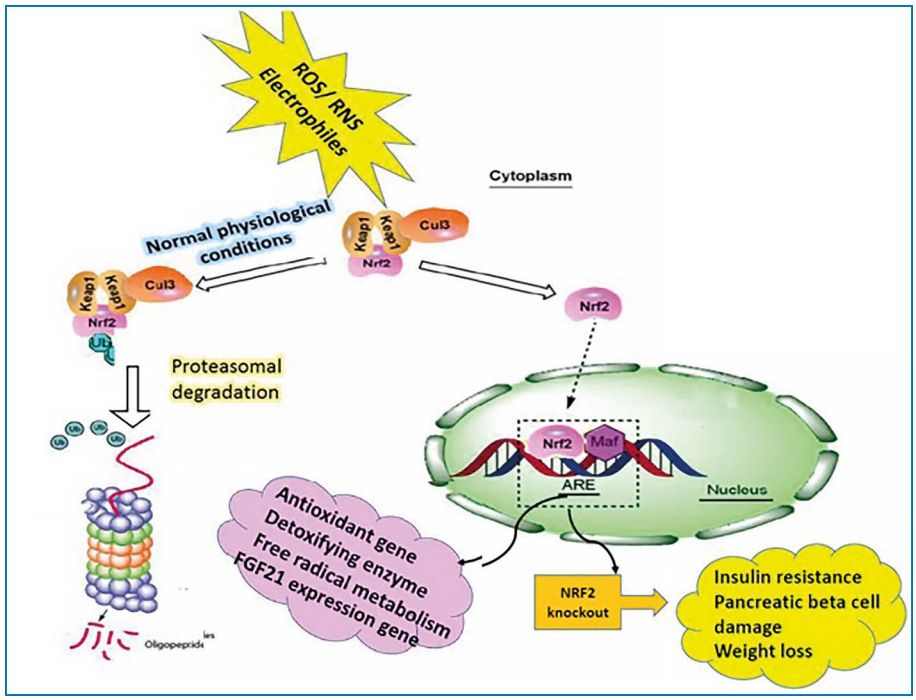

Figure 1. The NRF2/Keap1/ARE Pathway in Type 2 Diabetes Mellitus
(I) in the upstream region, Ark kinase causes phosphorylation and activation. (II) Under oxidative conditions, the Keap1 separates from NRF2 and NRF2 enters the nucleus. (III) In the non-oxidative state, the Keap1 binds to the NRF2 and ubiquitinates it, which is eventually degraded by the proteasome
ARE — antioxidant response element; Keap1 — Kelch like-ECH-associated protein 1; NRF2 — nuclear factor E2-related factor 2

NRF2 signaling pathway is one of the main mechanisms of cellular defense against oxidative stress; therefore, abnormal levels of NRF2 activity can contribute to cellular pathology. In this situation, the main function of NRF2 is attributed to its protective effects against oxidative stress via activation of numerous genes involved in antioxidative and anti-inflammatory defenses as well as those with repair functions, and metabolic regulation including NAD(P)H quinone oxidoreductase 1 (Nqo1), glutamate-cysteine ligase, sulfiredoxin 1 (SRXN1), thioredoxin reductase 1 (TXNRD1), heme oxygenase-1 (HMOX1, HO-1), glutathione S-transferase (GST), UDP-glucuronosyl-transferase (UGT), multidrug resistance-associated proteins (Mrps) [7, 8]. NRF2 also involves in induction of a set of drug-metabolizing enzymes such as NAD(P)H:quinone oxidoreductase 1 (NQO1) and glutathione S-transferase (GST) [1].

Several studies have indicated that the generation of reactive oxygen or nitrogen species (RONS) stimulated by hyperglycemia, can elevate the NRF2 expression [17]. Increased NRF2 level is able to counteract with the development of diabetic complications, via up-regulation of its downstream antioxidant genes such as NQO1, HO-1, and GST [17, 18] and downregulation of inflammatory pathway of the NF-κB [19]. NRF2/Keap1/ /ARE is a critical defensive pathway in the physiological protection of pancreatic β-cells against the accumulation of intracellular ROS and cell apoptosis, autophagy, and proteosomal degradation. Due to the destructive effect of oxidative stress on insulin secretion through a reduction in ATP production, the role of NRF2/Keap1/ /ARE pathway in insulin secretion seems to be important. Increased expression of NRF2 in pancreatic β-cells in the diabetic model of rodents indicates the protective role of NRF2 against oxidative stress in these cells [19]. NRF2 also regulates the expression of the catalytic subunits of proteasomes in pancreatic β-cells and are involved in the proteostasis activity of the endoplasmic reticulum, so that its defect reduces insulin secretion [20, 21].

NRF2 and induction of FGF21

In addition to preventing oxidative stress, NRF2 is also involved in metabolic homeostasis, including lipid metabolism and energy expenditure. Therefore, NRF2-knockout mice develop insulin resistance and weight loss. For example, adenosine monophosphate activated protein kinase (AMPK) as a key regulator of cellular metabolism plays a critical role in the maintenance of energy homeostasis. Activation of AMPK results in enhancement of glucose utilization [22]. NRF2 is suggested to regulate AMPK activity through phosphorylation of Thr-172. In contrast, the suppression of

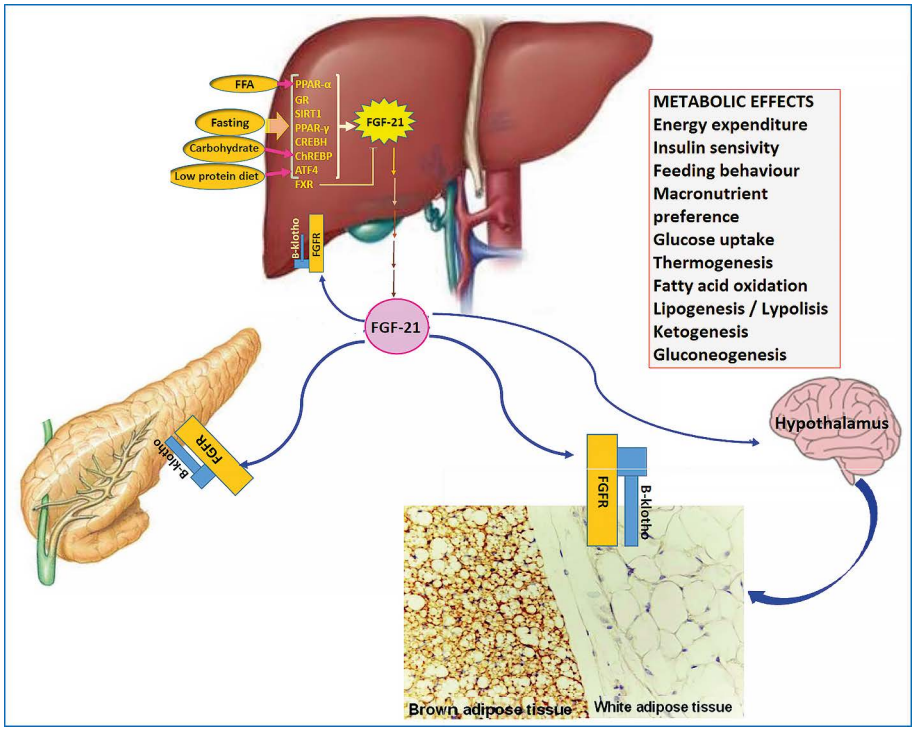

Figure 2. The Role of FGF21 in Metabolic Homeostasis
FGF21 — fibroblast growth factor 21

the NRF2 signaling attenuates AMPK phosphorylation (Thr-172) [23]. Therefore, it contributes to lower the blood glucose levels in the NRF2-induced animals [8] and significantly suppresses gluconeogenesis in diabetic rat model. Fibroblast growth factor 21 (FGF21) plays an important role in glucose and lipid metabolism and has an ARE sequence in its promoter. Studies have shown that NRF2 is also involved in regulating FGF21 expression [21]. Therefore, the FGF21 induction may be a mechanism through which NRF2 regulates expression levels of glycolysis-related genes [21, 24].

FGF21 is a 19 kDa protein with an in vivo half-life of 0.5 to 2 h. It belongs to the FGF family. Unlike other members of FDFs, FGF21 lacks the second heparin-like domain binding to the membrane, which enables FGF21 to leave the hepatocyte, enter the bloodstream and affect other organs. Its circulatory level is mainly due to hepatic secretion, so FGF21 is a hepatokine; however, it is also expressed in small amounts in adipose tissue, skeletal muscle, pancreas, brain and many other organs [31, 32]. As a peptide hormone, FGF21 binds to the FGF receptor (FGFR) complexed with β-klotho, a trans-membrane protein essential for FGF21-mediated signaling [32], and induces metabolic changes through intracellular signals of MAPKs, Raf1, Akt1 and STATs.

Under starvation conditions, GH (growth hormone) stimulates lipolysis in fat cells to release fatty acids. The liver uses glycerol and free fatty acids for gluconeogenesis and ketogenesis, respectively, through activation the nuclear hormone receptor-activating α-PP receptor (PPARα) (Fig. 2). PPARα activates the FGF21 promoter through PPARα response elements and increases hepatic and plasma levels of FGF21. FGF21, stimulates lipolysis in adipose tissue, and ketogenesis in liver, which in turn synergistically increases FGF21 production in the liver [25]. During starvation glucagon, catecholamines and glucocorticoids play an important role in this regard [24]. FGF21 protects the body from lipid-induced liver and muscle insulin resistance via a reduction in DAG (diacyl-glycerol) content, which reduces PKCε and PKCθ activation, leading to an improvement in insulin signaling [28].

Studies have shown that depletion of essential amino acids due to amino acid starvation or low protein diets also stimulates FGF21 expression, and when low protein is associated with a high carbohydrate intake, this induction is maximized [17] (Fig. 2). Low-protein diets activate the general control nonderepressible 2 (GCN2) kinase which is an amino acid sensor that induces a genetic program to effectively maintain cellular homeostasis. GCN2 activates the ATF4 and inactivates

the eIF2α through molecular phosphorylation [26]. The FGF21 promoter has several binding sites for ATF4; so after connecting ATF4 to the promoter, FGF21 is generated. Despite being valuable information on the effects of FGF21, little is known about its mechanism of its action or its regulation.

In the pancreas, FGF21 has a protective effect on the quality and function of β-cells. Studies have shown that deletion of FGF21 increases β-cell insufficiency and suppression of insulin secretion [27]{Gasser, 2017 #59}. Other studies in diabetic animals have shown the modulation of hyperglycemia, hyperlipidemia, decreased insulin resistance, and weight gain following FGF21 administration. In diabetes, FGF21 expression is increased to counteract the decrease in insulin secretion. Studies have shown that FGF21 increases the expression of insulin gene transcription factors, which depend on the induction of insulin expression through PI3K/Akt signaling [28, 29]. FGF21 has also been found to be positively associated with obesity, fasting insulin, and triglycerides, and negatively associated with high-density lipoprotein (HDL). FGF21 has also be found to be positively associated with fasting insulin, obesity, and triglycerides, and negatively associated with high-density lipoprotein (HDL) [30].

Cooperation of NRF2 and FGF21 in metabolic homeostasis

As it was mentioned above, FGF21 has an ARE sequence in its promoter which can be stimulated by NRF2. Furusawa et al. [31] in their study on Keap1--knockdown db/db mice reported NRF2 induction positively regulated hepatic FGF21 expression in liver and increased plasma FGF21 level. Although they considered FGF21 expression levels as a biomarker for the activity of Keap1-NRF2, FGF21 may be induced by other stimulators such as ATF4, which is another transcription factor and its expression increases under oxidative stress, starvation, and amino acid depletion. Therefore, FGF21 expression is increased in metabolic disorders such as obesity, diabetes, cardiovascular disease to maintain energy homeostasis [32, 33]. However, some evidence reported FGF21 may also involve in activation or upregulation of NRF2. Cheng et al. [34] in their study on type 1 diabetic nephropathy animal model founded that FGF21 is a stimulator for NRF2 activation trough PI3K/Akt/GSK--3β/Fyn pathway. FGF21 also inactivates phosphatase and tensin homolog (PTEN) that negatively regulates Akt signaling and activates AMPK. Activated AMPK improves NRF2-mediated antioxidative effect [35]. Yang et al. [36] in their study on high-fat-diet/STZ--induced type 2 diabetic model of both wild-type and

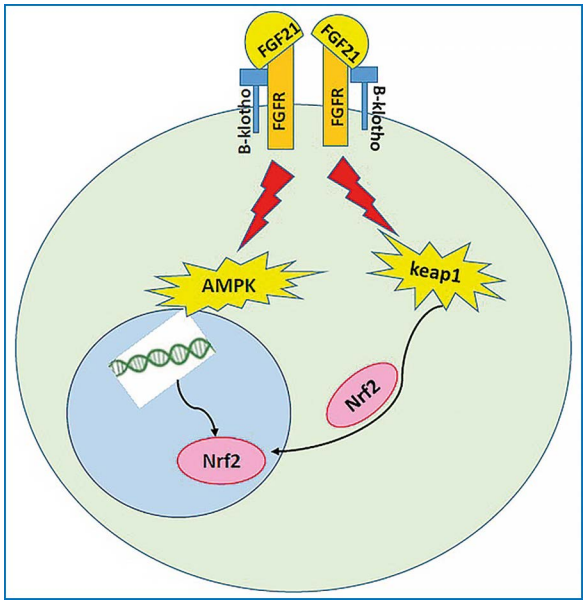

Figure 3. NRF2 Induction by FGF21
FGF21 — fibroblast growth factor 21; NRF2 — nuclear factor E2-related factor 2

FGF21-knockout mice treated with FGF21 reported that induction of antioxidative effect by both exogenous and endogenous FGF21 could be attributed to the activation of NRF2 through upregulation of a wide range of antioxidant genes. They founded FGF21 pharmacologically and physiologically inhibited type 2 diabetic lipotoxicity-induced cardiomyopathy by activating of both the antioxidant pathway mediated by AMPK-Akt2-NRF2 and the lipid-lowering effect of AMPK-ACC-CPT-1 in heart [36]. Yu et al. [33] stated that activation of FGFR1 by coupling with FGF21 may increase the binding of FGFR1 to Keapl. Subsequently, a decrease in the Keap1-NRF2 interaction leads to the release of NRF2 and ultimately an increase in the nuclear transfer of NRF2 from the cytoplasm (Fig. 3). However, it is not yet clear how NRF2 is delivered to the nucleus and whether FGF is involved.

The main hormonal function of FGF21 is to regulate glucose, fat and energy metabolism by increasing the glucose uptake into the adipose tissue, as well as lipolysis and the production of ketone bodies in the liver [37, 38]. Serum FGF21 levels increase with physical activity, lactation, colds and malnutrition. Hyperglycemia increases its hepatic expression by CREBP (carbohydrate response element-binding protein). Mitochondrial disorders that impair oxidative phosphorylation and decrease ATP production result in increased serum FGF21 [38, 39]. Anti-inflammatory effect of FGF21 is mediated by macrophages which are the targets for FGF21. It exerted an anti-inflammatory effect mainly

by enhancing NRF2-mediated anti-oxidant capacity and suppressing NF-κB signaling pathway [25].

Cooperation of NRF2 and FGF21 in preventing β-cell apoptosis

Hyperglycemia due to insulin resistance is the process that leads to the proliferation of β-cells and increase the biosynthesis and secretion of insulin [40, 41]. When insulin secretion cannot compensate for hyperglycemia and lead to β-cell destruction. The excessive production of reactive oxygen species during prolonged hyperglycemia is toxic to pancreatic β-cells, which reduces insulin production, impairs insulin secretion, and ultimately causes β-cell death and diabetes. However, in the early stages, β-cells inherently begin an effort to repair themselves. The most important repair mechanism is the activation of the cellular antioxidant system. NRF2, as the main regulator of antioxidant enzyme gene expression, is one of the essentials for controlling functional β-cells mass by maintaining redox balance, function, proliferation, and survival of β-cells. NRF2 activation preserves β-cell mass by reducing oxidative stress and inflammation and increasing insulin sensitivity. Human and animal studies have revealed an increase in NRF2 mRNA and protein and its nuclear accumulation following oxidative stress in most diabetic tissues [42–44]. On the other hand, in a study on a high-fat diet mouse model, it was found that insulin resistance was associated with increased levels of Keap1 and decreased levels of antioxidant enzymes in adipose tissue [45].

In the early stages of type 2 diabetes, hyperglycemia increases insulin synthesis and secretion by increasing the ratio of ATP to ADP. In such pathological conditions, protein loading in the endoplasmic reticulum (ER) may exceed the organelle's capacity to manage proper protein folding which may lead to ER stress. In response to ER stress, β-cells produce an adaptive response called unfolded protein response (UPR), which is controlled by the ER transmembrane proteins of inositol-requiring enzyme 1 (IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6) [46, 47]. PERK impairs protein translation and enhances the expression of a number of transcription factors, such as ATF4 (activating transcription factor 4). Although in hyperglycemia, β-cells are prone to ER stress and subsequent UPR, which may lead to β-cell death and diabetes [48]. During ER stress, PERK phosphorylates NRF2, which leads it to nuclear displacement and transcriptionally induces a surviving antioxidant response in β-cells [49]. PERK also acts as a protein sensor that inhibits mRNA translation and protein synthesis due to phosphorylation of eIF2 in order to reduce the ER stress load [50].

Protein-folding homeostasis in ER is highly sensitive to redox state. Alteration of redox equilibrium in both reducing and oxidizing states affects the formation of disulfide bonds, disrupts protein folding, and causes ER stress. During disulfide bond formation in nascent peptide, the thiol groups on cysteines are oxidized and H2O2 is produced as a byproduct [48]. Dysregulated in disulfide bond formation and ER stress may lead to ROS accumulation and oxidative stress. UPR or unfolded protein response in β-cells decreases insulin production and may lead to inflammation, cell apoptosis and diabetes.

ER stress increases FGF21 synthesis as a protective event. FGF21 is induced by ER stress through PERK-eIF2α-ATF4-dependent pathway [51]. Specific response elements of AARE1 and AARE2 (amino acid-responsive element) in the FGF21 promoter gene can be induced by ATF4, which in turn is stimulated by ER stress due to misfolded proteins or oxidative stress [52]. ATF4 also promotes the expression of β-Klotho.

FGF21 not only is a potent regulator of glucose homeostasis through increase in insulin secretion but also protects β-cells from apoptosis via extracellular signal-regulated kinase 1 and 2 (ERK1/2) and Akt signaling pathways. Coupling of FGF21 to its receptor causes rapid dimerization and autophosphorylation of the FGF receptor, which activates the ras/raf/MEK kinase signaling pathway. This eventually leads to the activation of ERK1/2 through phosphorylation. Activated ERK1/2 phosphorylate a large number of substrates localized in cytosol such as ribosomal S6 kinase (RSK), Mitogen- and stress-activated kinase 1/2 (MSK1/2) and MAPK-interacting kinases 1/2 (MNK1/2) [53]. ERK1/2 also transport to the nucleus and regulate the activities of several transcription factors [54] involved in regulation of cell metabolism and proliferation.

FGF21 can be considered as a stress response hormone due to inducing several antioxidant mechanisms. The three antioxidant mechanisms activated by FGF21 are 1-uncoupling protein 3 (UCP3) and superoxide dismutase-2 (SOD2) which reduce ROS levels; 2-ERK which suppresses the inflammatory pathway of NF-κB by activating CREB (cAMP responsive element binding protein); and 3-MAPK and p38 pathway that activates AMPK and reduces apoptosis. On the other hand, the activation of MAPK in turn inhibits the transcription of hepatic FGF21, suppresses the glucose 6 phosphatase gene and increases the hepatic gluconeogenesis [29, 55].

Role of NRF2 and FGF21 in prevention of diabetic complications

Diabetes is a highly heterogeneous disease with variable molecular, pathological, and clinical features. Overproduction of ROS in diabetes leads to harmful

cellular events, such as the formation of advanced glycation end products (AGEs) and upregulation of the receptor for AGEs (RAGE), activation of protein kinase C (PKC), the polyol pathway, hexosamine pathway [56]. Many studies have reported the protective effects of NRF2 and FGF21 activation on the complications of diabetes, such as diabetic nephropathy, cardiomyopathy, and retinopathy [58]. Upregulation of NRF2 and its downstream antioxidant genes in response to hyperglycemia and oxidative stress regulate the cellular detoxification response and redox status, as well as providing a protective action against various oxidative stresses and injuries. The increased risk of acute ischemic and nephrotoxic kidney injury in NRF2 deficiency suggests the protective role of this transcription factor as a potential therapeutic target. This protection is partly due to an endogenous antioxidant pathway. FGF-21, which plays an important role in regulating glucose and fat metabolism, appears to be a pharmacologically good option to compensate for insulin depletion in the treatment of diabetes and prevention of its complications. However, studies in human and animal cell lines have shown that although NRF2 activation is achieved by acute stimulation of high glucose [59], prolonged exposure to hyperglycemia interferes with NRF2 antioxidant signaling and exposes cells to more severe oxidative damage [57, 58].

Although amino acid starvation or low protein diets is a more important stimulus for FGF21 gene expression than energy deprivation, FGF21 is also elevated in other contexts such as fasting, overfeeding, and high-carbohydrate diets. Wente et al. [37] found that FGF21 promotes the expression of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) gene in the islands of db/db mice. Since SNARE (soluble NSF attachment protein receptor) is a major regulator of insulin secretion, FGF21 may increase insulin production and secretion through the SNARE and the phosphatidylinositol 3-kinase (PI3K)/ /Akt signaling pathway. However, the most effect of FGF21 is on adipose tissue, leading to decreased blood glucose levels, increased insulin sensitivity, weight loss, and decreased serum lipids. Oxidative stress has been shown to regulate the PI3K/Akt, the pathway that plays a significant role in cell survival signaling and is involved in critical biological responses such as calcium signaling, cell growth, differentiation, apoptosis, and insulin signaling [59]. Previous studies on various inducers such as hemin, tert-butyl hydroquinone (tBH), and proxynitrite, reported that the PI3K/Akt pathway is necessary for NRF2-ARE-dependent protection against oxidative stress [40, 60]. Wang et al. [59] stated that NRF2 nuclear translocation is regulated by the PI3K/ /Akt pathway. Obesity is an excessive accumulation of adipose tissue that usually occurs due to increased energy consumption and decreased physical activity. Adipose tissue not only acts as an energy storage organ but also, as an endocrine gland, regulates metabolic homeostasis through the secretion of biologically active compounds. Dyslipidemia, hyperglycemia, insulin resistance, and hypertension are among the most common pathological conditions associated with obesity, leading to metabolic diseases such as type 2 diabetes, nonalcoholic steatohepatitis, and metabolic syndrome. Several researches have reported an association between NRF2 and obesity in lab animals [61, 62]. Studies in NRF2 knockout mice have shown a lean phenotype [63, 64]. In addition to inducing antioxidant and detoxification target genes, NRF2 directly or indirectly regulates groups of tissue-specific genes that are specific to the metabolism or synthesis of fatty acids and other fats [61]. Most of the effects of NRF2 in this regard are inhibitory, but their mechanism is not well understood. NRF2 induction in liver involves a reduction in lipid biosynthesis and hepatic lipid levels [65]. Overall, in addition to the protective effect against oxidative stress and its associated diseases, NRF2 has important role in long-term adaptation to metabolic conditions, such as responding to calorie restriction, as well as controlling lipid metabolism in normal and high-fat diets.

As mentioned earlier, FGF21 is a peptide hormone that is mainly expressed and secreted in the liver and adipose tissue, regulates glucose and lipid metabolism, and induces insulin sensitivity. FGF21 increases lipid catabolism and mitochondrial oxidative activity by inducing lipolysis and oxidation of fatty acids, which can be associated with total body energy expenditure and increased thermogenesis in brown adipose tissue and white adipose tissue [30]. Such a decrease in serum triglycerides and lipid storage in the liver and skeletal muscle by FGF21 protects the body against lipid-induced insulin resistance. Samms et al. reported that treatment of obese, hyperglycemic, insulin-resistant and leptin-deficient B6-ob/ob mice with FGF21 could normalize hyperglycemia despite markedly elevated endogenous FGF21 levels. FGF21 also prevents the development of fatty pancreas, pancreatitis, fatty liver, and steatohepatitis, thereby preventing advanced pathologies such as pancreatic duct adenocarcinoma or liver cancer [66].

An increase in endogenous FGF21 levels, as seen in high-fat diets may be an anti-obesity condition against obesity which is associated with an increase in free fatty acids turnover and reduction in lipogenesis and glucose output. Therefore, obesity may be due to FGF21-resist-

Table 1. Collaboration between NRF2 and FGF21 in Metabolic Homeostasis and Preventing Apoptosis and Diabetes Complications

	Explanation	Ref
Cooperation of NRF2 and FGF21 in metabolic homeostasis	NRF2 induction positively regulates hepatic FGF21 expression in oxidative stress, starvation, and amino acid depletion conditions	[31]
	FGF21 is a stimulator for NRF2 antioxidant activity trough PI3K/Akt/GSK-3β/Fyn pathway	[32, 33]
	FGF21 inhibits type 2 diabetic lipotoxicity-induced cardiomyopathy by activating of both the antioxidant pathway mediated by AMPK-Akt2-NRF2 and the lipid-lowering effect of AMPK-ACC-CPT-1 in heart	[34]
Cooperation of NRF2 and FGF21 in preventing β-cell apoptosis	NRF2 activation preserves β-cell mass by reducing oxidative stress and inflammation and increasing insulin sensitivity	[40–42]
	FGF21 is induced by ER stress through PERK-eIF2α-ATF4-dependent pathway as a potent regulator of glucose homeostasis and protective factor against β-cells apoptosis *via* ERK1/2 and Akt signaling pathways	[49, 50]
	FGF21 activated ERK1/2 phosphorylates a large number of substrates localized in cytosol such as ribosomal S6 kinase (RSK), Mitogen- and stress-activated kinase 1/2 (MSK1/2) and MAPK-interacting kinases 1/2 (MNK1/2) and transports to the nucleus and regulate the activities of several transcription factors involved in regulation of cell metabolism and proliferation	[51, 52]
	FGF21 activates antioxidant mechanisms of uncoupling protein 3 (UCP3) and superoxide dismutase-2 (SOD2) which reduce ROS levels; ERK which suppresses the inflammatory pathway of NF-κB by activating CREB (cAMP responsive element binding protein); and MAPK and p38 pathway that activates AMPK and reduces apoptosis	[27, 53]
Role of NRF2 and FGF21 in prevention of diabetic complications	Upregulation of NRF2 and its downstream antioxidant genes in response to hyperglycemia and oxidative stress regulate the cellular detoxification response and redox status, as well as providing a protective action against various oxidative stresses and injuries	[56]
	FGF21 effects on adipose tissue, leading to decreased blood glucose levels, increased insulin sensitivity, weight loss, and decreased serum lipids	[36, 57]
	NRF2 directly or indirectly regulates groups of tissue-specific genes that are specific to the metabolism or synthesis of fatty acids and other fats	[59, 63]
	NRF2 induction in liver involves a reduction in lipid biosynthesis and hepatic lipid levels	[63, 64]
	FGF21 increases lipid catabolism and mitochondrial oxidative activity by inducing lipolysis and oxidation of fatty acids protecting the body against lipid-induced insulin resistance	[27]
	FGF21 induces ERK1/2 phosphorylation in adipose tissue as an important signal for lipolysis inhibiting TG accumulation during adipogenesis and improving systemic insulin and glucose tolerance	[65]
	FGF21 increases insulin-independent glucose uptake into adipocytes by inducing GLUT1 expression through β-klotho-ERK1/2-Elk-1/SRF signaling cascade	[65, 66]
	FGF21 inhibits pro-inflammatory factors such as TNF-α, IL-6, IL-1B, and MCP	[65]

AMPK — AMP-activated kinase; ARE — antioxidant response element; ER — endoplasmic reticulum; ERK — extracellular signal-regulated kinase; FGF21 — fibroblast growth factor 21; IL — interleukin; Keap1 — Kelch like-ECH-associated protein 1; MAPK — mitogen-activated protein kinase; NRF2 — nuclear factor E2-related factor 2; PERK — PKR-like ER kinase; PI3K — phosphatidylinositol 3-kinase; ROS — reactive oxygen species; TG — triglycerides; TNF-α — tumor necrosis factor α

ant conditions that are associated with elevated FGF21 blood levels [68]. Studies have shown that exogenous treatment of FGF21 induces ERK1/2 phosphorylation in adipose tissue. Activated ERK1/2 acts as an important signal for lipolysis and inhibits TG accumulation during adipogenesis and improves systemic insulin and glucose

tolerance. Studies have reported that FGF21 increases insulin-independent glucose uptake into adipocytes by inducing GLUT1 expression through β-klotho-ERK1/2-Elk-1/SRF signaling cascade, and a highly conserved cis-element within GLUT1 promoter [67]. Although ERK1/2 activity is essential for the early stages of adipogenesis, it must subsequently be inhibited to induce cell differentiation by PPARγ. Non-phosphorylated PPARγ is the main stimulator of adipocyte differentiation and its phosphorylation by ERK1/2 reduces transcriptional activity and inhibits differentiation [68].

Another important factor in the pathogenesis of diabetes is the chronic inflammation of adipose tissue through inflammatory agents. The inhibitory effects of FGF21 on many pro-inflammatory factors such as TNF-α, IL-6, IL-1B, and MCP1 [67], make it one of the appropriate therapeutic targets for diabetes.

Clinical implications

NRF2 and FGF21 can be considered as attractive therapeutic targets to control metabolic diseases. Because several studies have been shown that FGF21 administration in obese and/or diabetic models increase energy intake, insulin sensitivity and glucose tolerance, and reduce hepatic storage and serum triglyceride levels, and causes weight loss. Its short half-life (0.5–2 h), low intrinsic stability, and high aggregation propensity make its drug production difficult [69]. However, researchers have tried to produce long-acting analogs of FGF21 and agonist monoclonal antibodies to form the FGFR1-β-klotho complex. Several FGF21 analogs and mimics have been designed that are in the testing phase. Other approaches to improve the pharmacological properties of FGF21 have been described, including antibody fusion, and nanoparticles preparation to increase half-life, disulfide bonds to increase molecular stability, and recombinant forms for protease resistance. What has been observed in these trials so far is a significant improvement in dyslipidemia, fatty liver, and serum markers of liver fibrosis in patients with non-alcoholic steatohepatitis [66–68]. However, barriers to drug treatment with these FGF21 mimics include possible resistance to FGF21 in obesity, the presence of endogenous metabolizing enzymes for FGF21, and the presence of interspecific changes in the FGF21 molecule that make it difficult to generalize results to human physiology [69].

Conclusions

Table 1 summarizes some important cooperation of NRF2 and FGF21 in hemostasis. Impaired glucose and lipid homeostasis, insulin resistance and chronic inflammation are important complications of diabetes. FGF21 and NRF2 can be considered as attractive biomarkers for the diagnosis of specific metabolic diseases as well as therapeutic targets for controlling diabetic complications. Although the regulatory role of NRF2 and FGF21 in metabolic disorders is well established, most studies of therapeutic interventions based on NRF2 and FGF21 have been conducted in animal models, which may not be directly applicable to humans. Therefore, further clinical studies are needed to determine the efficacy of NRF2 and FGF21 in diabetic patients, so that they can be considered as therapeutic targets in drug design.

Conflict of interest

None declared.

REFERENCES

1. Zhang M, An C, Gao Y, et al. Emerging roles of Nrf2 and phase II antioxidant enzymes in neuroprotection. Prog Neurobiol. 2013; 100: 30–47, doi: 10.1016/j.pneurobio.2012.09.003, indexed in Pubmed: 23025925.
2. Li B, Liu S, Miao L, et al. Prevention of diabetic complications by activation of Nrf2: diabetic cardiomyopathy and nephropathy. Exp Diabetes Res. 2012; 2012: 216512, doi: 10.1155/2012/216512, indexed in Pubmed: 22645602.
3. Alizadeh-Fanalou S, Babaei M, Hosseini A, et al. Effects of Securigera Securidaca seed extract in combination with glibenclamide on antioxidant capacity, fibroblast growth factor 21 and insulin resistance in hyperglycemic rats. J Ethnopharmacol. 2020; 248: 112331, doi: 10.1016/j.jep.2019.112331, indexed in Pubmed: 31655149.
4. Babaei M, Alizadeh-Fanalou S, Nourian A, et al. Evaluation of testicular glycogen storage, FGF21 and LDH expression and physiological parameters of sperm in hyperglycemic rats treated with hydroalcoholic extract of Securigera Securidaca seeds, and Glibenclamide. Reprod Biol Endocrinol. 2021; 19(1): 104, doi: 10.1186/s12958-021-00794-1, indexed in Pubmed: 34233693.
5. Ma Q. Role of nrf2 in oxidative stress and toxicity. Annu Rev Pharmacol Toxicol. 2013; 53: 401–426, doi: 10.1146/annurev-pharmtox-011112-140320, indexed in Pubmed: 23294312.
6. Suzuki T, Yamamoto M. Stress-sensing mechanisms and the physiological roles of the Keap1-Nrf2 system during cellular stress. J Biol Chem. 2017; 292(41): 16817–16824, doi: 10.1074/jbc.R117.800169, indexed in Pubmed: 28842501.
7. Yu C, Xiao JH. The Keap1-Nrf2 System: A Mediator between Oxidative Stress and Aging. Oxid Med Cell Longev. 2021; 2021: 6635460, doi: 10.1155/2021/6635460, indexed in Pubmed: 34012501.
8. Mitsuishi Y, Motohashi H, Yamamoto M. The Keap1-Nrf2 system in cancers: stress response and anabolic metabolism. Front Oncol. 2012; 2: 200, doi: 10.3389/fonc.2012.00200, indexed in Pubmed: 23272301.
9. Yamamoto T, Suzuki T, Kobayashi A, et al. Physiological significance of reactive cysteine residues of Keap1 in determining Nrf2 activity. Mol Cell Biol. 2008; 28(8): 2758–2770, doi: 10.1128/MCB.01704-07, indexed in Pubmed: 18268004.
10. Bryan HK, Olayanju A, Goldring CE, et al. The Nrf2 cell defence pathway: Keap1-dependent and -independent mechanisms of regulation. Biochem Pharmacol. 2013; 85(6): 705–717, doi: 10.1016/j.bcp.2012.11.016, indexed in Pubmed: 23219527.
11. Zhao J, Zhang B, Li S, et al. Mangiferin increases Nrf2 protein stability by inhibiting its ubiquitination and degradation in human HL60 myeloid leukemia cells. Int J Mol Med. 2014; 33(5): 1348–1354, doi: 10.3892/ijmm.2014.1696, indexed in Pubmed: 24626801.

12. Saito R, Suzuki T, Hiramoto K, et al. Characterizations of Three Major Cysteine Sensors of Keap1 in Stress Response. Mol Cell Biol. 2016; 36(2): 271–284, doi: 10.1128/MCB.00868-15, indexed in Pubmed: 26527616.
13. O'Connell MA, Hayes JD. The Keap1/Nrf2 pathway in health and disease: from the bench to the clinic. Biochem Soc Trans. 2015; 43(4): 687–689, doi: 10.1042/BST20150069, indexed in Pubmed: 26551713.
14. da Costa RM, Rodrigues D, Pereira CA, et al. Nrf2 as a Potential Mediator of Cardiovascular Risk in Metabolic Diseases. Front Pharmacol. 2019; 10: 382, doi: 10.3389/fphar.2019.00382, indexed in Pubmed: 31031630.
15. Chowdhry S, Zhang Y, McMahon M, et al. Nrf2 is controlled by two distinct β-TrCP recognition motifs in its Neh6 domain, one of which can be modulated by GSK-3 activity. Oncogene. 2013; 32(32): 3765–3781, doi: 10.1038/onc.2012.388, indexed in Pubmed: 22964642.
16. Sun Z, Chin YE, Zhang DD. Acetylation of Nrf2 by p300/CBP augments promoter-specific DNA binding of Nrf2 during the antioxidant response. Mol Cell Biol. 2009; 29(10): 2658–2672, doi: 10.1128/MCB.01639-08, indexed in Pubmed: 19273602.
17. Jiang T, Huang Z, Lin Y, et al. The protective role of Nrf2 in streptozotocin-induced diabetic nephropathy. Diabetes. 2010; 59(4): 850–860, doi: 10.2337/db09-1342, indexed in Pubmed: 20103708.
18. Yarahmadi A, Khademi F, Mostafavi-Pour Z, et al. In-Vitro Analysis of Glucose and Quercetin Effects on m-TOR and Nrf-2 Expression in HepG2 Cell Line (Diabetes and Cancer Connection). Nutr Cancer. 2018; 70(5): 770–775, doi: 10.1080/01635581.2018.1470654, indexed in Pubmed: 29781726.
19. McEvoy B, Sumayao R, Slattery C, et al. Cystine accumulation attenuates insulin release from the pancreatic β-cell due to elevated oxidative stress and decreased ATP levels. J Physiol. 2015; 593(23): 5167–5182, doi: 10.1113/JP271237, indexed in Pubmed: 26482480.
20. Schaap FG, Kremer AE, Lamers WH, et al. Fibroblast growth factor 21 is induced by endoplasmic reticulum stress. Biochimie. 2013; 95(4): 692–699, doi: 10.1016/j.biochi.2012.10.019, indexed in Pubmed: 23123503.
21. Kharitonenkov A, Wroblewski VJ, Koester A, et al. The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. Endocrinology. 2007; 148(2): 774–781, doi: 10.1210/en.2006-1168, indexed in Pubmed: 17068132.
22. Shaw RJ, Kosmatka M, Bardeesy N, et al. The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. Proc Natl Acad Sci U S A. 2004; 101(10): 3329–3335, doi: 10.1073/pnas.0308061100, indexed in Pubmed: 14985505.
23. Meakin PJ, Chowdhry S, Sharma RS, et al. Susceptibility of Nrf2-null mice to steatohepatitis and cirrhosis upon consumption of a high-fat diet is associated with oxidative stress, perturbation of the unfolded protein response, and disturbance in the expression of metabolic enzymes but not with insulin resistance. Mol Cell Biol. 2014; 34(17): 3305–3320, doi: 10.1128/MCB.00677-14, indexed in Pubmed: 24958099.
24. Ye D, Wang Y, Li H, et al. Fibroblast growth factor 21 protects against acetaminophen-induced hepatotoxicity by potentiating peroxisome proliferator-activated receptor coactivator protein-1α-mediated antioxidant capacity in mice. Hepatology. 2014; 60(3): 977–989, doi: 10.1002/hep.27060, indexed in Pubmed: 24590984.
25. Yu Y, He J, Li S, et al. Fibroblast growth factor 21 (FGF21) inhibits macrophage-mediated inflammation by activating Nrf2 and suppressing the NF-κB signaling pathway. Int Immunopharmacol. 2016; 38: 144–152, doi: 10.1016/j.intimp.2016.05.026, indexed in Pubmed: 27276443.
26. Carraro V, Maurin AC, Lambert-Langlais S, et al. Amino acid availability controls TRB3 transcription in liver through the GCN2/eIF2α/ATF4 pathway. PLoS One. 2010; 5(12): e15716, doi: 10.1371/journal.pone.0015716, indexed in Pubmed: 21203563.
27. Zhang J, Weng W, Wang K, et al. The role of FGF21 in type 1 diabetes and its complications. Int J Biol Sci. 2018; 14(9): 1000–1011, doi: 10.7150/ijbs.25026, indexed in Pubmed: 29989062.
28. Pan Y, Wang B, Zheng J, et al. Pancreatic fibroblast growth factor 21 protects against type 2 diabetes in mice by promoting insulin expression and secretion in a PI3K/Akt signaling-dependent manner. J Cell Mol Med. 2019; 23(2): 1059–1071, doi: 10.1111/jcmm.14007, indexed in Pubmed: 30461198.
29. Wondrak GT, Villeneuve NF, Lamore SD, et al. The cinnamon-derived dietary factor cinnamic aldehyde activates the Nrf2-dependent antioxidant response in human epithelial colon cells. Molecules. 2010; 15(5): 3338–3355, doi: 10.3390/molecules15053338, indexed in Pubmed: 20657484.
30. Zhang X, Yeung DCY, Karpisek M, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes. 2008; 57(5): 1246–1253, doi: 10.2337/db07-1476, indexed in Pubmed: 18252893.
31. Furusawa Y, Uruno A, Yagishita Y, et al. Nrf2 induces fibroblast growth factor 21 in diabetic mice. Genes Cells. 2014; 19(12): 864–878, doi: 10.1111/gtc.12186, indexed in Pubmed: 25270507.
32. Iizuka K, Takeda J, Horikawa Y. Glucose induces FGF21 mRNA expression through ChREBP activation in rat hepatocytes. FEBS Lett. 2009; 583(17): 2882–2886, doi: 10.1016/j.febslet.2009.07.053, indexed in Pubmed: 19660458.
33. Yu Z, Lin Li, Jiang Y, et al. Recombinant FGF21 Protects Against Blood-Brain Barrier Leakage Through Nrf2 Upregulation in Type 2 Diabetes Mice. Mol Neurobiol. 2019; 56(4): 2314–2327, doi: 10.1007/s12035-018-1234-2, indexed in Pubmed: 30022432.
34. Cheng Y, Zhang J, Guo W, et al. Up-regulation of Nrf2 is involved in FGF21-mediated fenofibrate protection against type 1 diabetic nephropathy. Free Radic Biol Med. 2016; 93: 94–109, doi: 10.1016/j.freeradbiomed.2016.02.002, indexed in Pubmed: 26849944.
35. Zhang C, Huang Z, Gu J, et al. Fibroblast growth factor 21 protects the heart from apoptosis in a diabetic mouse model via extracellular signal-regulated kinase 1/2-dependent signalling pathway. Diabetologia. 2015; 58(8): 1937–1948, doi: 10.1007/s00125-015-3630-8, indexed in Pubmed: 26040473.
36. Yang H, Feng A, Lin S, et al. Fibroblast growth factor-21 prevents diabetic cardiomyopathy via AMPK-mediated antioxidation and lipid-lowering effects in the heart. Cell Death Dis. 2018; 9(2): 227, doi: 10.1038/s41419-018-0307-5, indexed in Pubmed: 29445083.
37. Wente W, Efanov AM, Brenner M, et al. Fibroblast growth factor-21 improves pancreatic beta-cell function and survival by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways. Diabetes. 2006; 55(9): 2470–2478, doi: 10.2337/db05-1435, indexed in Pubmed: 16936195.
38. Inagaki T, Dutchak P, Zhao G, et al. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. Cell Metab. 2007; 5(6): 415–425, doi: 10.1016/j.cmet.2007.05.003, indexed in Pubmed: 17550777.
39. Liu M, Cao H, Hou Y, et al. Liver Plays a Major Role in FGF-21 Mediated Glucose Homeostasis. Cell Physiol Biochem. 2018; 45(4): 1423–1433, doi: 10.1159/000487568, indexed in Pubmed: 29462809.
40. Li MH, Cha YN, Surh YJ. Peroxynitrite induces HO-1 expression via PI3K/Akt-dependent activation of NF-E2-related factor 2 in PC12 cells. Free Radic Biol Med. 2006; 41(7): 1079–1091, doi: 10.1016/j.freeradbiomed.2006.06.010, indexed in Pubmed: 16962933.
41. Wang L, Chen Y, Sternberg P, et al. Essential roles of the PI3 kinase/Akt pathway in regulating Nrf2-dependent antioxidant functions in the RPE. Invest Ophthalmol Vis Sci. 2008; 49(4): 1671–1678, doi: 10.1167/iovs.07-1099, indexed in Pubmed: 18385090.
42. Golpour P, Nourbakhsh M, Mazaherioun M, et al. Improvement of NRF2 gene expression and antioxidant status in patients with type 2 diabetes mellitus after supplementation with omega-3 polyunsaturated fatty acids: A double-blind randomised placebo-controlled clinical trial. Diabetes Res Clin Pract. 2020; 162: 108120, doi: 10.1016/j.diabres.2020.108120, indexed in Pubmed: 32194222.

43. Sireesh D, Dhamodharan U, Ezhilarasi K, et al. Association of NF-E2 Related Factor 2 (Nrf2) and inflammatory cytokines in recent onset Type 2 Diabetes Mellitus. Sci Rep. 2018; 8(1): 5126, doi: 10.1038/s41598-018-22913-6, indexed in Pubmed: 29572460.
44. Zhao S, Ghosh A, Lo CS, et al. Nrf2 Deficiency Upregulates Intrarenal Angiotensin-Converting Enzyme-2 and Angiotensin 1-7 Receptor Expression and Attenuates Hypertension and Nephropathy in Diabetic Mice. Endocrinology. 2018; 159(2): 836–852, doi: 10.1210/en.2017-00752, indexed in Pubmed: 29211853.
45. Chartoumpekis DV, Palliyaguru DL, Wakabayashi N, et al. Nrf2 deletion from adipocytes, but not hepatocytes, potentiates systemic metabolic dysfunction after long-term high-fat diet-induced obesity in mice. Am J Physiol Endocrinol Metab. 2018; 315(2): E180–E195, doi: 10.1152/ajpendo.00311.2017, indexed in Pubmed: 29486138.
46. Sano R, Reed JC. ER stress-induced cell death mechanisms. Biochim Biophys Acta. 2013; 1833(12): 3460–3470, doi: 10.1016/j.bbamcr.2013.06.028, indexed in Pubmed: 23850759.
47. Lindner P, Christensen SB, Nissen P, et al. Cell death induced by the ER stressor thapsigargin involves death receptor 5, a non-autophagic function of MAP1LC3B, and distinct contributions from unfolded protein response components. Cell Commun Signal. 2020; 18(1): 12, doi: 10.1186/s12964-019-0499-z, indexed in Pubmed: 31987044.
48. Malhotra JD, Kaufman RJ. Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? Antioxid Redox Signal. 2007; 9(12): 2277–2293, doi: 10.1089/ars.2007.1782, indexed in Pubmed: 17979528.
49. Cunha DA, Cito M, Carlsson PO, et al. Thrombospondin 1 protects pancreatic β-cells from lipotoxicity via the PERK-NRF2 pathway. Cell Death Differ. 2016; 23(12): 1995–2006, doi: 10.1038/cdd.2016.89, indexed in Pubmed: 27588705.
50. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell. 2010; 140(6): 900–917, doi: 10.1016/j.cell.2010.02.034, indexed in Pubmed: 20303879.
51. Kim SH, Kim KH, Kim HK, et al. Fibroblast growth factor 21 participates in adaptation to endoplasmic reticulum stress and attenuates obesity-induced hepatic metabolic stress. Diabetologia. 2015; 58(4): 809–818, doi: 10.1007/s00125-014-3475-6, indexed in Pubmed: 25537833.
52. Schaap FG, Kremer AE, Lamers WH, et al. Fibroblast growth factor 21 is induced by endoplasmic reticulum stress. Biochimie. 2013; 95(4): 692–699, doi: 10.1016/j.biochi.2012.10.019, indexed in Pubmed: 23123503.
53. Joshi S, Platanias LC. Mnk kinase pathway: Cellular functions and biological outcomes. World J Biol Chem. 2014; 5(3): 321–333, doi: 10.4331/wjbc.v5.i3.321, indexed in Pubmed: 25225600.
54. Kurosu H, Choi M, Ogawa Y, et al. Tissue-specific expression of betaKlotho and fibroblast growth factor (FGF) receptor isoforms determines metabolic activity of FGF19 and FGF21. J Biol Chem. 2007; 282(37): 26687–26695, doi: 10.1074/jbc.M704165200, indexed in Pubmed: 17623664.
55. Gómez-Sámano MÁ, Grajales-Gómez M, Zuarth-Vázquez JM, et al. Fibroblast growth factor 21 and its novel association with oxidative stress. Redox Biol. 2017; 11: 335–341, doi: 10.1016/j.redox.2016.12.024, indexed in Pubmed: 28039838.
56. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010; 107(9): 1058–1070, doi: 10.1161/CIRCRESAHA.110.223545, indexed in Pubmed: 21030723.
57. Bitar MS, Al-Mulla F. A defect in Nrf2 signaling constitutes a mechanism for cellular stress hypersensitivity in a genetic rat model of type 2 diabetes. Am J Physiol Endocrinol Metab. 2011; 301(6): E1119–E1129, doi: 10.1152/ajpendo.00047.2011, indexed in Pubmed: 21878664.
58. Mozzini C, Garbin U, Stranieri C, et al. Endoplasmic reticulum stress and Nrf2 repression in circulating cells of type 2 diabetic patients without the recommended glycemic goals. Free Radic Res. 2015; 49(3): 244–252, doi: 10.3109/10715762.2014.997229, indexed in Pubmed: 25511473.
59. Wang L, Chen Y, Sternberg P, et al. Essential roles of the PI3 kinase/Akt pathway in regulating Nrf2-dependent antioxidant functions in the RPE. Invest Ophthalmol Vis Sci. 2008; 49(4): 1671–1678, doi: 10.1167/iovs.07-1099, indexed in Pubmed: 18385090.
60. Lee JM, Hanson JM, Chu WA, et al. Phosphatidylinositol 3-kinase, not extracellular signal-regulated kinase, regulates activation of the antioxidant-responsive element in IMR-32 human neuroblastoma cells. J Biol Chem. 2001; 276(23): 20011–20016, doi: 10.1074/jbc.M100734200, indexed in Pubmed: 11274155.
61. Shin S, Wakabayashi J, Yates MS, et al. Role of Nrf2 in prevention of high-fat diet-induced obesity by synthetic triterpenoid CDDO-imidazolide. Eur J Pharmacol. 2009; 620(1-3): 138–144, doi: 10.1016/j.ejphar.2009.08.022, indexed in Pubmed: 19698707.
62. Yu Z, Shao W, Chiang Y, et al. Oltipraz upregulates the nuclear factor (erythroid-derived 2)-like 2 [corrected](NRF2) antioxidant system and prevents insulin resistance and obesity induced by a high-fat diet in C57BL/6J mice. Diabetologia. 2011; 54(4): 922–934, doi: 10.1007/s00125-010-2001-8, indexed in Pubmed: 21161163.
63. Pi J, Leung L, Xue P, et al. Deficiency in the nuclear factor E2-related factor-2 transcription factor results in impaired adipogenesis and protects against diet-induced obesity. J Biol Chem. 2010; 285(12): 9292–9300, doi: 10.1074/jbc.M109.093955, indexed in Pubmed: 20089859.
64. Chartoumpekis DV, Ziros PG, Psyrogiannis AI, et al. Nrf2 represses FGF21 during long-term high-fat diet-induced obesity in mice. Diabetes. 2011; 60(10): 2465–2473, doi: 10.2337/db11-0112, indexed in Pubmed: 21852674.
65. Tanaka Y, Aleksunes LM, Yeager RL, et al. NF-E2-related factor 2 inhibits lipid accumulation and oxidative stress in mice fed a high-fat diet. J Pharmacol Exp Ther. 2008; 325(2): 655–664, doi: 10.1124/jpet.107.135822, indexed in Pubmed: 18281592.
66. Samms RJ, Smith DP, Cheng CC, et al. Discrete Aspects of FGF21 In Vivo Pharmacology Do Not Require UCP1. Cell Rep. 2015; 11(7): 991–999, doi: 10.1016/j.celrep.2015.04.046, indexed in Pubmed: 25956583.
67. Ge X, Chen C, Hui X, et al. Fibroblast growth factor 21 induces glucose transporter-1 expression through activation of the serum response factor/Ets-like protein-1 in adipocytes. J Biol Chem. 2011; 286(40): 34533–34541, doi: 10.1074/jbc.M111.248591, indexed in Pubmed: 21846717.
68. Hu E, Kim JB, Sarraf P, et al. Inhibition of adipogenesis through MAP kinase-mediated phosphorylation of PPARgamma. Science. 1996; 274(5295): 2100–2103, doi: 10.1126/science.274.5295.2100, indexed in Pubmed: 8953045.
69. Geng L, Lam KSL, Xu A. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. Nat Rev Endocrinol. 2020; 16(11): 654–667, doi: 10.1038/s41574-020-0386-0, indexed in Pubmed: 32764725.