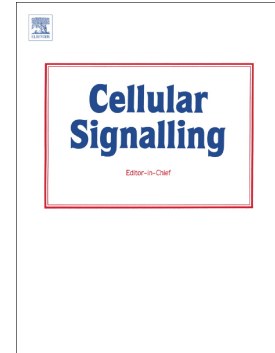


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REVIEW

Integrated stress response stimulates FGF21 expression: systemic enhancer of longevity

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Abstract

FGF21 is a multifunctional metabolic and stress hormone which is normally expressed in liver but cellular stress, e.g. mitochondrial or endoplasmic reticulum (ER) stress, can induce its expression and subsequent secretion from several mammalian tissues. The stress kinases of the integrated stress response (ISR) pathway stimulate the expression of FGF21 through the activation of ATF4 transcription factor, thus enhancing cellular stress resistance. The metabolic and stress-inducible transactivation mechanisms of *FGF21* gene are mostly mediated through separate pathways. FGF21 is an interorgan regulator which can alleviate many age-related metabolic and stress disorders, e.g. through the activation of AMPK signaling. FGF21 signaling is also involved in circadian and torpor regulation. Given that circulating FGF21 can attenuate organelle stress, e.g. mitochondrial and ER stresses, it resembles a stress-induced cell non-autonomous regulation of proteostasis and longevity present in model organisms. The overexpression of FGF21 can even extend the lifespan of mice, probably by improving the healthspan. We will clarify the positive and negative signaling mechanisms which control the stress-related expression of FGF21 through the ISR pathway. Moreover, we will examine the role of FGF21 as an interorgan coordinator of survival functions in metabolic and stress disorders. We conclude that FGF21 can be viewed as a cell non-autonomous enhancer of longevity in mammals.

1. Introduction

Fibroblast growth factor 21 (FGF21) is an endocrine member of FGF family which contains multifunctional signaling factors possessing a diversity of survival and developmental properties [1]. FGF21 is a coordinator of systemic energy metabolism; a topic which recently has been discussed in detail in several review articles [2,3]. In brief, FGF21 regulates the energy expenditure of the body by controlling the metabolism of glucose and lipids. For instance, FGF21 enhances glucose uptake into adipose tissues and thus decreases serum hyperglycemia. Moreover, FGF21 stimulates tissue free fatty acid (FFA) oxidation and thus it reduces the serum levels of FFA and LDL-cholesterol. Correspondingly, FGF21 inhibits gluconeogenesis and lipogenesis in liver. There is a significant crosstalk between FGF21 and insulin/IGF-1 in the control of energy metabolism, e.g. FGF21 administration improves insulin sensitivity in mice [4]. Circulating FGF21 stimulates the FGFR1/ β -klotho receptor complex which subsequently activates several signaling pathways, e.g. AMPK and ERK signaling [5,6]. The receptor components are expressed in a tissue and context-dependent manner, which is an important regulatory mechanism of FGF21 responses. In addition, FGF21 can also regulate energy metabolism by controlling the secretion of other hormones, e.g. adiponectin in adipose tissues and corticosteroids in the hypothalamic-pituitary-adrenal (HPA) axis [7,8]. Overall, FGF21 is an evolutionarily conserved, inducible endocrine factor which allows the organism to modify its energy metabolism to cope with different metabolic crises [9].

FGF21 is not only an energy metabolic regulator but it can also act as a stress hormone maintaining tissue homeostasis, in an autocrine, paracrine or endocrine fashion [10-12]. There is compelling evidence that the integrated stress response (ISR) pathway stimulates the expression of FGF21 (Section 2.2.). The ISR pathway is an evolutionarily conserved stress response pathway which strives to maintain cellular homeostasis and induces adaptation to many diverse stress stimuli [13]. There are also systemic mechanisms which coordinate interorgan adaptation to stresses, known as a cell non-autonomous mechanism in lower species (Section 3.1.). FGF21 can be viewed as an ideal cell non-autonomous messenger since organelle stress stimulates its expression and secretion from many peripheral tissues into the circulation, thus attempting to restore whole body homeostasis. There are

several studies indicating that a stress-induced increase in the level of circulating FGF21 can alleviate systemic metabolic and stress disorders and thus enhance healthspan (Section 4.2.). The overexpression of FGF21 can even extend the lifespan of mice, i.e. FGF21 seems to be a cell non-autonomous enhancer of longevity. First, we will describe the mechanisms of FGF21 expression through the ISR pathway in different tissues. Next we will examine how FGF21 acts as an interorgan messenger to coordinate survival functions in the body. Finally, we discuss observations indicating that FGF21 can inhibit organelle stress and alleviate age-related disorders and thus extend healthspan and lifespan of the organism.

2. Integrated stress response regulates the expression and secretion of FGF21

2.1. Integrated stress response (ISR)

The integrated stress response (ISR) refers to the convergence of several stress signaling pathways leading to the phosphorylation of eukaryotic translation initiation factor 2 α (eIF2 α) [13,14] (Fig. 1). There are four different eIF2 α -specific kinases which phosphorylate the eIF2 α subunit of the eIF2 complex [14,15]. This event preferentially stimulates the translation of stress-inducible mRNAs e.g. activating transcription factor 4 (ATF4) which subsequently augments the transcription of a specific set of stress-related genes, including the *FGF21* gene (Fig. 1). Conversely, the phosphorylation of eIF2 α protein represses general protein synthesis which is a common response encountered in the ISR [14]. The group of four eIF2 α kinases include protein kinase R (PKR), PKR-like endoplasmic reticulum kinase (PERK), general control non-depressible 2 (GCN2), and heme-regulated eIF2 α kinase (HRI) (Fig. 1). These kinases possess a homologous catalytic enzyme domain but the regulatory domains are distinct, allowing specific responses to different stress stimuli [15]. For instance, mitochondrial and ER stresses commonly activate the PERK/eIF2 α /ATF4 pathway, whereas GCN2 responds to the deprivation of amino acids and nutritional starvation (Fig. 1). PERK is a crucial sensor of misfolded proteins in ER and consequently can block protein synthesis by phosphorylating eIF2 α (Fig. 1). In this respect, PERK is an important element in the unfolded protein response of ER (erUPR) and thus able to restore ER homeostasis which can be disturbed by several stresses, e.g.

oxidative stress, hypoxia, and a deficiency of autophagic clearance [15-17]. GCN2 is the most ancient and widespread of the eIF2 α kinases, i.e. it is also present in yeast conferring tolerance to intracellular acid stress [18]. However, the main function of GCN2 is to respond to nutritional stress, especially amino acid deprivation (Fig. 1). B'chir et al. [19] demonstrated that amino acid starvation activated the GCN2-mediated increase in ATF4 expression and subsequently induced the expression of autophagy genes in mouse fibroblasts. A third eIF2 α kinase, PKR, is activated by viral infections if it encounters a double-stranded RNA insult, although recent studies have revealed other inducers, including oxidative stress and many cytokines and some growth factors [15]. PKR is not exclusively an eIF2 α kinase, since it can also stimulate many inflammatory pathways, e.g. via the formation of inflammasomes [20]. HRI has a crucial role in the maintenance of iron homeostasis and it can protect cells against metal overload, e.g. Pb-induced toxicity [21].

The phosphorylation of eIF2 α protein on Ser51 inhibits the formation of the pre-initiation complex of mRNA translation and thus it prevents subsequent protein synthesis [15,22]. However, the phosphorylated eIF2 α protein can enhance the translation of some mRNAs, such as that of ATF4, since the 5'UTR of their mRNAs contains distinct uORF sequences which preferentially allow the initiation of translation with the phosphorylated eIF2 α subunit [14,23]. ATF4 is a basic leucine zipper (bZIP) domain containing transcription factor which forms active homodimers but it can also heterodimerize with other bZIP factors, e.g. C/EBP γ , HIF-1 α , NRF2, PHD3 [13]. Given that amino acid deprivation induces the transcription of ATF4, the DNA binding site was called the amino acid response element (AARE) or C/EBP:ATF4 response element (CARE) [23,24]. ATF4 has a crucial role in the generation of adaptive responses and thus supports survival in the face of a variety of stresses. The main defence strategy is to alleviate the stress condition e.g. by activation of autophagy in amino acid deprivation [19,23], stimulation of antioxidant defences in oxidative stress [25], or inhibition of mRNA translation and elevation of protein folding capacity in ER stress [26]. The intensity of stress and its duration, i.e. is it acute or chronic, can affect the outcome of ISR activation; either it rescues cells or triggers their apoptotic death. If homeostasis cannot be restored, ATF4 can induce cellular

apoptosis by stimulating the expression of C/EBP homologous protein (CHOP) which can execute cell death through a variety of mechanisms [13] (Fig. 1).

There are negative feedback mechanisms which prevent an excessive activation of the eIF2 α /ATF4 pathway during stress and they can trigger cellular recovery [27,28]. ATF4 stimulates the expression of GADD34, a protein phosphatase 1 (PP1) regulatory subunit 15A, which interacts with the catalytic unit of PP1. GADD34 binds to the eIF2 α protein and subsequently PP1 dephosphorylates it, thus relieving translational repression and preventing possible apoptosis (Fig. 1). It seems that energy metabolic stress can also suppress the function of the ISR pathway, probably preventing the ATF4-induced apoptosis in excessive stress. Ghosh et al. [29] demonstrated that eIF2 α protein interacted with SIRT1, a NAD⁺-dependent Sirtuin-type deacetylase, which inhibited the phosphorylation of eIF2 α protein (Fig. 1). Moreover, SIRT1 activation prevented the expression of ATF4 induced by proteasome inhibition, indicating that SIRT1 was able to repress ISR signaling [30]. Recently, Prola et al. [31] revealed that SIRT1 activation attenuated the ER stress-induced PERK/eIF2 α signaling by deacetylating eIF2 α protein and thus rescued mouse cardiomyocytes from apoptotic cell death. It is known that eIF2 α has a crucial role in the control of a cell's fate, deciding between adaptation and death in stress and thus disturbances in the regulation of eIF2 α phosphorylation might augment pathogenesis in many diseases, e.g. fatty liver disease [32].

2.2. Stimulation of *FGF21* expression via the ISR pathway

Several studies have identified two functional AARE/CARE response elements in the promoter of *FGF21* gene [10,33]. The activation of eIF2 α /ATF4 signaling stimulates the transcription of *FGF21* gene to combat many stresses, e.g. amino acid deprivation [33,34], ER stress [10,12], and mitochondrial disturbances [35-37]. There are observations indicating that the eIF2 α kinases can induce the stimulation of the *FGF21* transcription in a stress-specific manner, i.e. PERK is activated by ER stress and mitochondrial disorders [10,35], whereas GCN2 is induced by protein restriction [34]. In addition, Touvier et al. [38] observed that the muscle-specific overexpression of mitochondrial dynamin-related protein 1 (DRP1) induced the activation of the eIF2 α /ATF4/*FGF21* pathway through

the stimulation of PKR, subsequently inhibiting protein synthesis and muscle growth. Moreover, Zarei et al. [39] reported that the down-regulation of PPAR β/δ expression in hepatocytes, e.g. in animals fed a high-fat diet, activated HRI which consequently increased the expression of FGF21 via the ISR signaling. These studies clearly demonstrated that FGF21 is the target of ISR signaling and furthermore, that FGF21 can attenuate cellular stresses (Section 3.2.).

In addition to PERK, ER stress also stimulates two other stress pathways, i.e. the IRE1 α -XBP1 and ATF6 pathways, which induce the transcriptional response of erUPR [40]. Interestingly, Jiang et al. [41] demonstrated that XBP1 controlled the expression of the *FGF21* gene through the ER stress response element (ERSE) located in the promoter of the human *FGF21* gene. The IRE1-XBP1 pathway can directly target the FGF21 gene without activating the ISR pathway (Fig. 1). The IRE1 α -XBP1 branch has many significant functions in glucose and lipid metabolism [42], some of which might be mediated through an increased expression of FGF21. In conclusion, it seems that the expression of FGF21 can be stimulated through multiple stress response pathways and subsequently FGF21 can attenuate stress at the cellular, tissue, and organismal levels in auto-, para-, and endocrine fashions.

2.3. Stress-inducible expression of *FGF21* in multiple tissues

2.3.1. Liver

In normal physiological conditions, liver is the major source of expression and secretion of FGF21 [43]. However, given that the *FGF21* gene is a stress-inducible gene, its expression and secretion can be significantly stimulated in many tissues, e.g. in skeletal and cardiac muscles (Fig. 2). The nutritional state regulates the expression of hepatic FGF21 via the PPAR α signaling [44]. The promoter of the human *FGF21* gene contains the PPAR α response element (PPRE) which is also involved in the induction of the fasting-induced expression of FGF21 [45]. Badman et al. [44] demonstrated that a high-fat, low-carbohydrate ketogenic diet substantially increased the expression and secretion of FGF21 from mouse liver. The diet significantly increased lipid oxidation and ketogenesis as well as enhanced triglyceride clearance from liver. Moreover, a carbohydrate-rich diet

stimulated the hepatic expression of FGF21 through the activation of carbohydrate response element binding protein (ChREBP), both in mice and humans [9,46]. Especially, fructose ingestion induced a robust expression of FGF21 and increased its secretion from mouse liver [46]. These studies indicate that a nutritional crisis, either fasting or overfeeding, can stimulate the expression of FGF21 in liver.

In contrast to the energy metabolic regulation of FGF21 expression, dietary amino acid deprivation stimulates the expression of hepatic FGF21 through the GCN2-driven ISR pathway [33,34]. Uncharged tRNAs activate GCN2 kinase which subsequently phosphorylates eIF2 α inhibiting protein synthesis [47] (Fig. 1). De Sousa-Coelho et al. [33] demonstrated that a leucine deficiency induced the expression of FGF21 in mouse liver through the binding of ATF4 factor to the AARE sites present in the promoter of *FGF21* gene. Laeger et al. [34] also revealed that a low-protein diet stimulated the expression of FGF21 via the GCN2-activated ISR pathway in rat liver although no increase was detected in skeletal muscle or white adipose tissue. There is compelling evidence that a methionine restriction (MR) diet can induce a robust increase in the hepatic expression and secretion of FGF21 in an ATF4-dependent manner [48]. An MR diet exerts several beneficial effects in hepatic glucose and lipid metabolism which can improve healthspan and even extend lifespan [49]. Liver ER stress linked to the PERK and XBP1-activated FGF21 expression is involved in many energy metabolic disturbances, e.g. hepatosteatosis associated with obesity, as well as oxidative stress and toxic insults [10,50]. Impaired autophagy and mitochondrial disturbances also trigger ER stress and stimulate the expression of hepatic FGF21 [36,51]. Subsequently, an increased expression of FGF21 attenuates many energy metabolic disorders in the body (Section 4.2.). Interestingly, ER stress also stimulated the expression of β -klotho via the ATF4 signaling in mouse liver [52]. This might improve the auto/paracrine signaling of secreted FGF21 and thus provide a positive feedback mechanism to alleviate stress-induced hepatic disturbances.

2.3.2. Adipose tissues

Adipose tissues contain three different types of adipose cells, i.e. white, brown, and beige/brite adipocytes [53]. White and brown adipocytes differentiate through separate pathways from mesenchymal cells. White adipose tissues (WAT) accumulate fat and they have a role in energy

storage, whereas brown adipose tissues (BAT) are rich in mitochondria and they are specialized in thermogenesis. White adipocytes can be transdifferentiated to beige/brite or brown adipocytes in a process called the browning of WAT which increases the amount of mitochondria and subsequently augments the metabolism of fat deposits to be combusted in thermogenesis. Given that the browning of WAT increases energy expenditure, this type of activation of WAT as well as the control of BAT functions have a significant therapeutic potential in obesity and other metabolic diseases [54,55]. There are many studies which have revealed that both cold-exposure and β -adrenergic stimulation can induce the expression of FGF21 in BAT [56,57]. Hondares et al. [56] demonstrated that the cold-exposure increased the FGF21 expression in BAT and elevated the level of FGF21 in mouse circulation (Fig. 2). They also reported that norepinephrine increased the expression and secretion of FGF21 by brown adipocytes in culture. Furthermore, Fisher et al. [57] reported that both the cold-induced and pharmacologically supplemented FGF21 was able to provoke the browning of WAT by increasing the expression of PGC-1 α and UCP1. The thermogenic adaptation was impaired in the FGF21-knockout mice indicating that FGF21 has a crucial role in the browning of WAT and adaptive thermogenesis. Chronic adrenergic stress can also induce the browning of subcutaneous WAT in humans [58]. In addition to thermogenesis, BAT also is an important endocrine organ secreting important adipokines, e.g. adiponectin and neuregulin 4, which control systemic metabolism [59]. Thus, FGF21 can enhance stress resistance by inducing thermogenesis and promoting the secretion of adipokines from BAT.

Currently, the signaling pathways of WAT browning and adaptive thermogenesis still need to be clarified, although several hormonal and environmental agents can trigger thermogenic activation [54,55]. β -Adrenergic stimulation is known to activate the cAMP/PKA/p38MAPK signaling pathway which triggers a downstream activation of the ATF2 transcription factor [56]. ATF2 is a crucial stress-related transcription factor e.g. inducing adaptive responses to amino acid deficiency in collaboration with the GCN2/ATF4 axis [60]. ATF2, activated by JNK and p38MAPK signaling, binds to the AARE site where it promotes histone acetylation thus enhancing the subsequent transcription by ATF4, e.g. in the promoter of the *CHOP* gene [61]. Interestingly, there are studies indicating that

ATF2 can induce stress-related epigenetic changes in the heterochromatin structure which are heritable to the next generation [62]. It is known that mitochondrial stress can also induce the expression of FGF21 in adipose tissue and subsequently increase the browning of WAT in an ATF4-dependent manner [36]. Keipert et al. [37] reported that an increased secretion of FGF21 from the skeletal muscles of tg-UCP1 mice (Section 2.3.3) induced the browning of subcutaneous WAT. This indicates that circulating FGF21, either from stressed liver or skeletal muscles, is able to induce the browning process and subsequent thermogenesis in adipose tissues. On the other hand, it is known that ER stress, as induced by the accumulation of fat into adipose tissues, is associated with increased inflammation. BAT is remarkably susceptible to pro-inflammatory cytokines, e.g. IL-1 β and TNF- α , which down-regulated the expression of BAT-specific markers and β -klotho protein, a co-receptor of FGFR1 [63]. TNF- α administration also markedly inhibited the expression of β -klotho protein in adipocytes [64]. It seems that inflammation is a potent repressor of the browning process of WAT and thermogenesis since it can generate FGF21 resistance by inhibiting FGF21 signaling (Section 4.4.).

2.3.3. Skeletal and cardiac muscles

There is abundant evidence indicating that FGF21 is a myokine which can be induced by several stresses and subsequently secreted into the circulation [37,65,66] (Fig. 2). In skeletal muscles, especially mitochondrial disorders stimulate the expression of FGF21 and increase its secretion. There are several experimental models of muscle mitochondrial disturbances that are characterized by a significant increase in the expression of FGF21, such as transgenic mice with overexpression of uncoupling protein 1 (UCP1) [37], a mutation in the mitochondrial replicative helicase Twinkle [67], and a depletion of iron-sulfur clusters [68]. Kim et al. [36] demonstrated that a skeletal muscle-specific deletion of *Atg7* gene which induced disturbances in autophagy and mitochondrial functions, stimulated the ATF4-dependent expression of FGF21 in mouse skeletal muscles. The expression of FGF21 was also induced through the activation of ISR pathway in the transgenic UCP1 mice [37]. Moreover, the ER stress of skeletal muscles stimulated FGF21 expression through the activation of the eIF2 α /ATF4 pathway [69,70]. Miyake et al. [70] demonstrated that the overactivation of PERK induced the ATF4-dependent expression and secretion of FGF21 from mouse skeletal muscles. It

seems that physical exercise clearly stimulated [71] or at least stimulated to some extent [72] the expression of FGF21 in mouse skeletal muscles, whereas surprisingly the exercise-induced expression of FGF21 was more robust in liver [71,72]. FGF21 has a specific role in the differentiation of skeletal muscle fibers since MYOD, a myogenic transcription factor, can bind to the promoter of *FGF21* gene and increase its expression during myogenic differentiation [65,73]. Recently, Liu et al. [73] demonstrated that an increased expression of FGF21 in muscle cells promoted the formation of oxidative muscle fibers via the activation of the FGF21/SIRT1/AMPK/PGC1 α pathway. This observation is in contrast with many studies indicating that the skeletal muscles of adult animals do not express β -klotho protein and thus they should not be able to respond to the secreted FGF21 [37,74] (Fig. 2). Ost et al. [75] also revealed that the loss of FGF21 in muscles did not affect their ability to mount a metabolic rescue from mitochondrial stress and thus it seems that there is no auto/paracrine regulation of FGF21 in skeletal muscles. However, it is not known whether β -klotho is expressed in muscles during development or regeneration of muscle injuries. For instance, transgenic UCP1 mice displayed an increase in the expression of β -klotho in skeletal muscles [37].

In cardiac muscle, FGF21 is expressed normally at a low level but this becomes increased by many stresses and diseases, e.g. ischemic insults [76], mitochondrial stress [77], ER stress [78], fasting [78], and obesity [76]. Several studies have also reported that during stress heart muscle secreted FGF21 and thus controlled its own rescue process via auto/paracrine mechanisms [76,79] (Fig. 2). Interestingly, myocardial ischemia also stimulated the expression of FGF21 in mouse liver and adipose tissue [80]. Subsequently, an increased serum/extracellular level of FGF21 enhanced the cardiac protection and augmented remodelling by inhibiting oxidative stress and inflammatory response [79] as well as improving energy metabolic homeostasis [78].

2.3.4. Brain

The administration of FGF21 has significant neuroprotective responses in the brain [81-83] and moreover, it can stimulate the HPA axis to combat organismal stress (Sections 2.2. and 3.2.). Although FGF21 is expressed in distinct loci in the brain, rather little is known about its induction by stress and involvement in brain disorders. It is known that mood stabilizers, e.g. lithium and valproate [81, 84],

as well as some histone deacetylase (HDAC) inhibitors [83,84] can upregulate FGF21 expression in brain. Wang et al. [83] demonstrated that stroke significantly reduced the expression level of FGF21 in ischemic rat cortex and striatum. Treatment with tubastatin A, an HDAC6 inhibitor, could reverse the stroke-induced downregulation of FGF21 and concomitantly alleviated functional deficits. Hayashi et al. [85] reported that a transient ischemia in brain triggered ER stress and activated the ISR pathway which subsequently stimulated the expression of CHOP, a down-stream target of ISR, and provoked neuronal apoptosis. It seems that the activation of the ISR pathway can either induce stress resistance or trigger apoptosis in a context- and tissue-specific manner which means that FGF21 might be an important modifier of the outcome of ISR activation (Fig. 1).

3. Cell non-autonomous communication regulates stress responses between tissues

One fundamental question on the aging process is whether it is regulated in a cell-autonomous and/or cell non-autonomous manner. Cellular senescence and senescence-associated secretion of inflammatory mediators represent a cell or tissue autonomous mechanism, whereas systemic stress signaling represents a cell non-autonomous process [86-88]. The endocrine function of FGF21 is not a typical hormonal response since it can be induced in several tissues, probably in every tissue, in association with stress and it can target many tissues directly, through a specific receptor complex, or indirectly e.g. by inducing the secretion of adipokines. In this respect, the function of FGF21 resembles cell non-autonomous stress signalling, a process known to have an impact on the aging process in lower species [87,89-91].

3.1. Experiments with model organisms

Cell non-autonomous interorgan communication is an evolutionarily conserved mechanism through which distal tissues can exchange stress-related information to maintain homeostasis throughout the whole organism [88,92]. In 2011, Durieux et al. [89] demonstrated in *Caenorhabditis elegans* that the mitochondrial stress-induced mtUPR in the nervous system generated a similar mtUPR in intestine, indicating that the stimulation of mtUPR could be transferred between tissues. Subsequently, Taylor and Dillin [93] reported that the expression of constitutively active neuronal

XBP-1, a marker of ER stress, induced an increase in the erUPR of distal non-neuronal tissues in *C. elegans*. Interestingly, the cell non-autonomous interorgan transmission of erUPR did not trigger the mtUPR, revealing the specificity of interorgan communication. It is not only UPR signaling that can be transferred between tissues, since Ulgherait et al. [90] observed that the induction of brain autophagy through the AMPK/Atg1 activation also stimulated autophagy in intestinal epithelium in *Drosophila*. Moreover, the intestine-specific AMPK activation promoted autophagy in brain and skeletal muscles. They reported that the tissue-specific activation of AMPK repressed the expression of *Drosophila* insulin-like peptide 2 (DILP2) in both brain and in the circulation. Simultaneously with the repression of DILP2, the expression of 4E-BP increased in brain and peripheral tissues [90]. Interestingly, in the transgenic mice with overexpression of 4E-BP1 in their skeletal muscles, there was a reduction of WAT deposition as well as the protection of mice against hepatic steatosis [94]. The phenotype of the tg-4E-BP1 mice was associated with a substantial increase in the level of FGF21 in both muscles and circulation. Currently, it is known that systemic stress can induce the expression and secretion of several bioactive molecules which mediate the signaling circuits between tissues. Two peptides are especially interesting; mitochondrial DNA coded peptides humanin [95,96] and MOTS-c [97] which exerts several cell non-autonomous metabolic and survival effects in mammals. Furthermore, catecholamines [91] and neuropeptide FLP-2 [98] have been identified as cell non-autonomous messengers in *C. elegans*. It is not surprising that the induction of both erUPR and mtUPR triggers the cell non-autonomous defence, since the maintenance of organismal proteostasis has a fundamental role in the regulation of healthspan and lifespan.

A phenomenon called transcellular chaperone signaling is an interesting example of cell non-autonomous regulation [99,100]. van Oosten-Hawle et al. [99] demonstrated that the muscle-specific induction of HSP90 expression repressed the activation of heat-shock factor-1 (HSF-1) in other tissues of *C. elegans*. This inhibition of transcriptional activity of HSF-1 reduced the global induction of the heat-shock response (HSR), as evaluated by an increased HSP70 expression. It was observed that an increased expression of HSP90 in one individual tissue could induce a cell non-autonomous induction of HSP90 in many other tissues. Moreover, the knockdown of HSP90 gene in muscle cells evoked a

global induction of the HSR. Currently, the mechanism of transcellular chaperone signaling is unresolved although it seems to involve the activation of PHA-4, an ortholog of FOXA [99]. The studies on the cell non-autonomous regulation of proteostasis are important since a loss of the global maintenance of proteostasis is a common feature of the aging process [101].

There is compelling evidence that the cell non-autonomous signaling induced by cell organelle stress, i.e. mitochondrial or ER stress, can enhance cellular survival and longevity [89,91,93,102]. Moreover, the AMPK-induced autophagy can be transmitted in a cell non-autonomous manner which will directly improve the maintenance of whole-body proteostasis and extend the lifespan of *Drosophila* [90]. The transcellular chaperone signaling observed in *C. elegans* intended to maintain organismal proteostasis, might have a crucial role in the aging process and age-related diseases, if also present in mammals. Interestingly, mitochondrial and ER stresses are the major inducers of the ISR (Section 2.1) although currently it is not known whether the activation of eIF2 α /ATF4 pathway could be linked to the cell non-autonomous stress regulation. Nevertheless, FGF21 does possess several of the properties required of a cell non-autonomous messenger; (i) its expression is induced by organelle stresses, (ii) it is secreted from stressed tissues, and (iii) it can improve the metabolic homeostasis and survival of target tissues through either direct or indirect signaling mechanisms.

3.2. FGF21 is an interorgan regulator

The metabolic activity of FGF21 signaling in target tissues is dependent on the presence of functional FGFR1/ β -klotho complexes. FGFR1 is expressed at medium or high level in human tissues except in liver where it is not present (Human Protein Atlas). Given that liver is the major producer of circulating FGF21, the lack of FGFR1 expression is a rational mechanism preventing the auto/paracrine metabolic responses of FGF21 in liver. The expression of β -klotho is also absent in some tissue, e.g. in skeletal muscles. However, the expression of β -klotho can be induced or repressed in tissues and this can modify the capacity of FGF21 to evoke metabolic and survival responses. For instance, ER stress can stimulate the expression of hepatic β -klotho protein by activating ATF4-dependent signaling [52]. In contrast, inflammatory cytokines and nuclear protein Rev-erb α , a

circadian regulator, are important repressors of β -*klotho* gene expression [64,103,104]. There is compelling evidence indicating that the liver coordinates global metabolism, both at rest and in times of stress, through multiorgan crosstalk by secreting FGF21 as well as some other hepatokines [105]. Adipose tissue is a crucial target of secreted hepatic FGF21 generating both energy metabolic and hormonal responses [3,106]. In addition to the browning of WAT and thermogenesis in BAT (Section 2.3.2.), FGF21 stimulates the expression and secretion of adiponectin from adipose tissues, consequently affecting tissues throughout the body [8,106,107]. Adiponectin has a key role in the regulation of global energy metabolism elicited by FGF21, e.g. in the control of glucose and lipid metabolism and insulin sensitivity. However, BonDurant et al. [108] demonstrated that during chronic FGF21 exposures, FGF21 can control energy homeostasis, e.g. insulin sensitivity and glucose metabolism, in an adiponectin-independent manner. There is a mutual FGF21-adiponectin feedback mechanism between liver and adipose tissues since for instance, adiponectin can suppress hepatic inflammation and fibrosis as well as augment hepatic regeneration [109,110]. Moreover, adipose tissues can secrete exosomes containing microRNAs, e.g. miR-99b, which inhibit the expression of hepatic *FGF21* gene [111]. It seems that exosomes can also be involved in the interorgan regulation of FGF21 signaling.

Interestingly, in mice, a jeopardized tissue, e.g. ischemic myocardium, can stimulate the expression of FGF21 in liver and adipose tissue and consequently the FGF21 secreted by liver can alleviate myocardial injuries and enhance myocardial recovery [80]. FGF21, either acting in an auto/paracrine or an endocrine manner, has a key role in cardioprotection not only against ischemic injuries but also to combat other pathological processes, e.g. cardiac hypertrophy, atherosclerosis, and diabetic cardiomyopathy [112] (Section 4.2.). Mounting evidence indicates that FGF21 is an important myokine and there is a coordinated regulation between skeletal muscles and adipose tissues [36,37,70,113]. Kim et al. [36] demonstrated that an autophagy deficiency in skeletal muscle increased FGF21 secretion and consequently it stimulated the lipid oxidation and browning of WAT. Keipert et al. [37] also reported that the elevated FGF21 secretion from the skeletal muscles of tg-UCP1 mice (Section 2.3.3.) induced the browning of WAT and also enhanced gluconeogenesis in liver. It is

recognized that there is a close crosstalk between muscles and adipose tissues in the regulation of whole-body energy metabolism [114].

Circulating FGF21 can also target hypothalamus in brain and thus regulate systemic energy metabolism, circadian rhythm, and stress responses [82]. There are two nuclei in hypothalamus, i.e. paraventricular nucleus (PVN) and suprachiasmatic nucleus (SCN), which translate the FGF21 message through complex neurocircuitry into hormonal responses. Moreover, FGF21 can stimulate in hypothalamus the neurons producing neuropeptide Y which consequently triggers a torpor-like hypothermia [115] (Section 3.3.). Liang et al. [116] revealed that FGF21 administration induced the synthesis of corticotropin-releasing hormone (CRH) in PVN locus which consequently activated the HPA axis and increased the release of corticosteroids to the circulation. Corticosteroids/glucocorticoids have a fundamental role in acute adaptation to stress, whereas chronic or aberrant signaling is associated with many metabolic disorders and pathological conditions [117]. Interestingly, the promoter of the *FGF21* gene contains the functional non-canonical response element for the glucocorticoid receptor (GRE) [118], thus corticosteroids themselves can directly activate the transcription of *FGF21* gene. It seems that there is a feed-forward loop between FGF21 and corticosteroids to facilitate the adaptation of the organism to stress. In addition, it is known that the FGF21-induced CRH stimulates sympathetic nerve activity which for instance, promoted thermogenesis in BAT thus increasing energy expenditure in mouse [119]. These studies indicate that the peripheral induction of FGF21 expression as a result of the activation of ISR can provoke a systemic stress response through the HPA axis.

3.3. *FGF21 is involved in circadian and torpor regulation*

The circadian rhythm involves a 24-hour daily oscillation of metabolic processes across the species [120]. The mammalian circadian system contains a central pacemaker, i.e. the SCN locus in hypothalamus, and peripheral circadian clocks almost in every cell. The SCN controls peripheral cellular clocks through neuronal and humoral signals in order to synchronize the body's metabolic functions and behavioral activities. Liver has a fundamental role in the coordination of circadian

timing of energy metabolism between tissues [121,122]. There is mounting evidence that the level of serum FGF21 oscillates in a day/night rhythm [123-125]. Currently, it is not clear whether FGF21 might mediate the circadian regulation of energy metabolism. Given that FGF21 has many crucial functions in the control of energy metabolism, one could speculate that FGF21 may be involved in the coordination of circadian metabolism in target tissues. For instance, hepatic PPAR α , a transactivator of FGF21 expression, is a target of CLOCK protein, a protein which controls the circadian rhythm in liver [126]. It is also known that FGF21 has signaling connections to some important regulators of circadian metabolism, e.g. AMPK [127] and REV-ERB α [128]. Adiponectin, a target gene of FGF21 signaling, is under the circadian regulation [129]. FGF21 might also participate in the circadian feedback responses since Bookout et al. [7] demonstrated that circulating FGF21 could control the function of SCN loci, e.g. it increased the level of serum corticosteroids. There is abundant evidence that during the aging process, circadian regulation is impaired and thus the maintenance and resetting the timing of circadian clocks, e.g. by feeding regiments, could be an innovative way to improve healthspan and longevity [130].

Torpor is a short-term hibernation-like condition in which an animal's metabolic rate, body temperature, and physical activity can be reduced for weeks or for shorter periods, e.g. as in daily torpor [131,132]. Inagaki et al. [45] observed that the body temperature of transgenic mice overexpressing FGF21 was lower than that of wild-type mice. Interestingly, fasting promoted the induction of torpor in FGF21 transgenic mice but not in their wild-type counterparts. Chu and Swoap [133] demonstrated that wild-type mice fed a bezafibrate diet for two weeks experienced spontaneous episodes of torpor. Given that bezafibrate is an agonist of PPAR α and it has been shown to elevate the level of FGF21 in both liver and serum, it could be argued that FGF21 is playing a fundamental role in torpor production. Currently, the mechanisms of torpor induction are unclear although contributions from FGF21, AMPK, and SIRT1 signaling [131] as well as hormonal changes [132] have been proposed. Ishida [115] discussed the evidence indicating that PPAR α has an essential role in torpor initiation since it stimulated the expression of FGF21 which consequently induced the expression of

neuropeptide Y (NPY). This signaling pathway was mediated through the hypothalamic SCN locus. It seems that FGF21 is a versatile messenger in the regulation of diverse cell non-autonomous functions.

4. FGF21 is cell non-autonomous regulator of longevity in mammals

4.1. FGF21 signaling is involved in regulation of longevity

The signaling mechanisms utilized by FGF21 are poorly understood but it does seem that FGF21 activates downstream signaling pathways in a tissue-specific and context-dependent manner. Moreover, FGF21 can stimulate the secretion of adiponectin and corticosteroids (Section 3.2.) which have their own signaling mechanisms and stress-related responses. Currently, it is known that the major signaling pathways of the FGFR1/ β -klotho complex are mediated through the AMPK, PI-3K/AKT/mTORC1, and RAS/RAF/ERK1/2 cascades [5,6,80]. Chau et al. [5] revealed that FGF21 controlled energy metabolism in adipocytes and mouse WAT through the activation of the AMPK/SIRT1/PGC-1 α pathway. AMPK is a crucial energy sensor which modulates energy expenditure by regulating glucose and lipid metabolism, e.g. by activating SIRT1 [5]. The metabolic profiles induced by FGF21 and AMPK activation are rather similar which indicates that AMPK signaling has a key role in the metabolic control induced by FGF21 [134]. The downstream targets of AMPK signaling involve PGC-1 α [5], a key regulator of mitochondrial metabolism, ULK1 [135], an inducer of autophagy, and NRF2/HO-1 [136], the main sensor of redox balance. Furthermore, AMPK signaling inhibits mTORC1 signaling and NF- κ B-induced inflammatory responses [137]. Interestingly, all these signaling cascades have recognized importance as enhancers of longevity [138-140].

The mTORC1 complex has a fundamental role in the regulation of the aging process and age-related diseases [139,141]. There are many genetic, pharmacological, and metabolic studies demonstrating that the reduction of mTORC1 activity increases the lifespan of model organisms and alleviates age-related pathological processes. Gong et al. [142] reported that virally delivered FGF21 inhibited the activity of mTORC1 in mouse liver and consequently improved hepatic insulin sensitivity and glucose homeostasis in mice fed with a high-fat, high-sucrose diet. The FGF21-induced

inhibition of mTORC1 was dependent on hepatic expression of β -klotho as well as the activity of TSC1 complex which indicates that AMPK activation might have been involved [134,143]. On the other hand, a constitutive, tissue-specific activation of mTORC1, by knocking out the *Tsc1* gene, revealed that mTORC1 activation stimulated the expression and secretion of FGF21 both in mouse liver [144] and skeletal muscle [69]. Cornu et al. [144] demonstrated that a liver-specific activation of mTORC1 induced FGF21 expression by promoting the expression of PGC-1 α . They observed that the activity of mTORC1 oscillated daily (Section 3.3.) affecting FGF21 secretion and thus body temperature, lipid metabolism, and locomotor activity of mice. A prolonged activation of mTORC1 in skeletal muscle triggered ER stress and the expression of FGF21 was induced through the PERK/eIF2 α /ATF4 pathway [69] (Section 2.2.). Moreover, Minard et al. [145] demonstrated that circulating FGF21 activated mTORC1 through the MAPK pathway in mouse adipose tissue. Consequently, mTORC1 stimulated adiponectin secretion and increased the expression of UCP1. There is convincing evidence that mitochondria have a crucial role in the control of mTORC1-regulated longevity [146]. For instance, it is known that in mice, mitochondrial uncoupling, as can be achieved by an increased expression of UCP proteins, can extend lifespan and alleviate age-related diseases [147].

Endocrine FGF21 cooperates with other hormones and growth factors to generate adaptive responses to stress and metabolic disturbances and in that way, it can also promote healthy aging. For instance, there is a mutual crosstalk between FGF21 and the hormones of the somatotrophic axis, i.e. growth hormone (GH) and insulin-like growth factor-1 (IGF-1). The somatotrophic pathway has a fundamental role in growth and development, but its excessive activity accelerates the aging process [148]. Interestingly, Inagaki et al. [149] demonstrated that transgenic mice overexpressing FGF21 displayed a hepatic GH resistance which decreased the secretion of IGF-1 from liver. Although the reduced level of serum IGF-1 impaired the growth of transgenic mice, these animals lived significantly longer than their normal counterparts (Section 4.3.). However, an acute treatment of mice with GH stimulated the expression of FGF21 in liver and increased the level of serum FGF21 [150]. The GH exposure activated the STAT5 signaling pathway in mouse liver which induced the

transcription of the *FGF21* gene [150]. It seems that there is a regulatory feedback mechanism between FGF21 and GH which might control longevity by inhibiting an overactive somatotrophic axis. We have recently clarified the different molecular mechanisms which could be involved in the FGF21-mediated healthspan and lifespan regulation [151].

4.2. *FGF21 attenuates age-related metabolic and stress disorders*

There is an extensive literature indicating that the pharmacological administration of FGF21 can alleviate many age-related metabolic and stress disorders. Since FGF21 increases energy expenditure, it is able to ameliorate obesity-associated disorders, e.g. fatty liver diseases and type 2 diabetes [152,153]. FGF21 has also therapeutic potential in cardiovascular diseases, e.g. its administration inhibited atherosclerosis [154] and protected against cardiac ischemia-reperfusion injuries [76]. FGF21 treatment also ameliorated inflammatory disorders in collagen-induced arthritis [155]. Moreover, Fu et al. [156] demonstrated that FGF21 exposure inhibited retinal and choroidal neovascularization in experimental mouse models of age-related macular degeneration. The suppression of angiogenesis was mediated by adiponectin and it was not dependent on VEGFA. Currently, there are several drug development programs striving to acquire therapeutic FGF21 mimetics which could activate the FGFR1/ β -klotho complex [157].

FGF21 is a stress hormone which aims to combat many pathological conditions in a cell non-autonomous manner. Kim et al. [36] demonstrated in mice that an impaired autophagy in skeletal muscles stimulated FGF21 expression and consequently increased the level of serum FGF21. Surprisingly, these mice displayed a decreased level of body fat which could be attributable to enhanced energy expenditure through increased fatty acid oxidation and browning of WAT. Moreover, these animals were protected against diet-induced obesity and insulin resistance and their phenotype resembled that of transgenic mice with overexpression of FGF21 (Section 4.3.). Wang et al. [51] revealed that the liver-specific lack of mitochondrial DRP1 protein triggered ER stress and stimulated the expression and secretion of FGF21. These mice also were lean and protected from high-fat diet

induced obesity. There is mounting evidence indicating that the circulating FGF21 can ameliorate ER stress in jeopardized target tissues and thus alleviate metabolic and stress disorders [12,158].

Since FGF21 is a fasting hormone, it might affect age-related diseases and be involved in the lifespan expansion encountered with caloric restriction (CR). In rodents, as well as in primates and humans, a moderate CR not only ameliorates age-related chronic diseases but it can also extend healthspan and lifespan [159,160]. Kuhla et al. [161] demonstrated that a lifelong CR of mice increased gradually the expression of FGF21 in liver and especially elevated the level of serum FGF21. CR also dramatically changed the hepatic lipid metabolism reducing lipogenesis and increasing lipolysis and ketogenesis. Recent studies have revealed that a low-protein nutrition and distinct amino acids restricted diets rather than CR are responsible for the increase in healthspan and might extend lifespan in mammals [33,34,162,163]. A low-protein chow and a methionine-restricted diet increased the level of serum FGF21 and improved the health of mice [34,48]. In addition, Fontana et al. [164] observed that serum IGF-1 concentrations were reduced in moderately protein-restricted humans. As discussed earlier (Section 2.3.1), amino acid shortage stimulates the GCN2-activated ISR which consequently can induce FGF21 expression in tissues. Given that plant-based diets contain a modest level of proteins, it has been speculated that these diets might increase the serum level of FGF21 and thus mediate multiple health benefits [165,166].

4.3. *FGF21 extends lifespan*

Inagaki et al. [45] established a transgenic mouse line which expressed the mouse *FGF21* gene under the control of an ApoE promoter (tg-FGF21). The hepatic mRNA expression of tg-FGF21 mice was about 50-fold higher than that of fasted wild-type mice [45], whereas the level of serum FGF21 was 5-fold elevated in tg-FGF21 mice in comparison with fasted control mice [149]. The transgenic mice were clearly smaller than their wild-type counterparts and they also lived significantly longer, i.e. their median survival time was extended by about 40% [167]. Screening of serum factors revealed that the concentrations of IGF-1 and insulin were substantially lower in tg-FGF21 mice than in wild-type mice. This indicates that the somatotrophic axis had become down-regulated in these transgenic mice which might explain their extended lifespan (Section 4.1.). The level of serum adiponectin was higher

in tg-FGF21 mice which might improve their healthspan. The concentrations of serum glucose and triglycerides were rather low in transgenic mice which implies that these animals enjoyed enhanced energy expenditure [167]. In addition to the beneficial effects on energy metabolism, an elevated level of FGF21 can also protect against immune senescence [168]. Youm et al. [168] observed that the involution of thymus, a common hallmark of aging, was significantly delayed in tg-FGF21 mice. The degeneration of thymus provokes functional decline in adaptive immunity, e.g. deficiencies in T cell functions. In addition, they reported that the knockout of the *FGF21* gene considerably enhanced the aging process of thymus. It is known that a low-grade inflammation can accelerate the aging process in mammalian tissues [169].

4.4. FGF21 resistance disturbs the healthy aging process

Interestingly, the serum level of FGF21 is significantly elevated in metabolic disorders, e.g. obesity, type 2 diabetes, and fatty liver disease [170,171]. Atherosclerosis and muscle mitochondrial myopathies also increase the serum concentration of FGF21 [67,172]. However, the situation is confusing since an increased level of serum FGF21 should prevent the appearance of metabolic disorders and furthermore, the administration of FGF21 at high pharmacological levels can alleviate these disorders. There is compelling evidence that chronic metabolic diseases are associated with FGF21 resistance, i.e. the downstream signaling from the FGFR1/ β -klotho complex becomes significantly depressed. Fisher et al. [173] demonstrated that obesity is a FGF21-resistant state in mouse liver and adipose tissues. They reported that in obese mice, the capacity of FGF21 to activate ERK1/2 was substantially diminished, reflecting FGF21 resistance. Currently, FGF21 resistance has been confirmed in many metabolic diseases, e.g. in type 2 diabetes [171]. There are observations indicating that the expression of β -klotho is reduced in metabolic diseases which impairs signaling through the FGFR1/ β -klotho complex [76,174]. Chronic inflammation, a phenomenon associated with metabolic and stress-related disorders, is a potent inhibitor of β -klotho expression [64,104]. The crucial role of β -klotho deficiency in FGF21 resistance was highlighted in an experiment which revealed that the overexpression of β -klotho increased the sensitivity of mouse adipose tissue to

FGF21 exposure and subsequently prevented the high-fat diet induced obesity [175]. Interestingly, Dong et al. [52] demonstrated that ER stress stimulated the expression of β -klotho in mouse liver through the ATF4-dependent (ISR) pathway. Keipert et al. [37] reported that the expression of β -klotho was increased through the ISR pathway in the liver, muscle, and WAT of tg-UCP1 mice (Section 2.3.3.). It seems that the expression of β -klotho protein has a crucial role in determining the sensitivity of tissues to FGF21 signaling, i.e. in the prevention of FGF21 resistance. However, Markan et al. [176] recently revealed that there are also distinct signaling mechanisms other than the down-regulation of β -klotho which contribute to FGF21 resistance in mouse WAT.

One interesting question is whether the aging process enhances the generation of FGF21 resistance which might expose tissues to metabolic diseases. Hanks et al. [177] revealed that the serum level of FGF21 increased linearly with aging in a healthy adult population. They studied several groups aged between 20-30 yrs to 65-80 yrs. The increase in the circulating level of FGF21 with aging was not dependent on changes in body composition, e.g. body mass index or total fat percent. The age-related increase in tissue stresses, e.g. decline in autophagy, mitochondrial disturbances, or ER stress, might stimulate the expression and secretion of FGF21 with aging. For instance, liver is prone to age-related degeneration [178]. Considering the role of FGFR1/ β -klotho receptor in FGF21 resistance, it is known that microRNA-34a (miR-34a) can inhibit the expression of β -klotho and FGFR1 [179,180]. The expression of miR-34a is significantly elevated in obesity [180] and coronary artery disease [181]. The expression of miR-34a also displayed a robust increase with aging in several rodent tissues [182,183] which might suppress the signaling of FGFR1/ β -klotho receptor and thus provoke aging-linked FGF21 resistance. Moreover, the aging process clearly reduces the responsiveness of AMPK activation [184], a downstream target of FGF21 signaling, and thus it could inhibit the expression of several metabolic genes with aging induced by the FGF21/AMPK pathway. Currently, the mechanisms of FGF21 resistance are very poorly understood at least in comparison to that of insulin resistance.

5. Conclusions

FGF21 is a multifunctional stress-inducible metabolic regulator which can promote tissue survival during stress conditions. The stress kinases of ISR pathway activate transcription factor ATF4 which subsequently induces the expression of FGF21. In contrast, the energy metabolic regulation of FGF21 transcription is mediated through the PPAR α signaling and some other metabolically regulated transcription factors. It seems that the metabolic and stress-related transactivation mechanisms of the *FGF21* gene are separated although the downstream signaling from the FGFR1/ β -klotho receptor, e.g. via AMPK activation, can control both metabolic and stress-related functions. There is convincing evidence that FGF21 is an interorgan regulator which can attenuate tissue stresses and induce adaptations against stress via systemic regulation. For instance, organelle stress, e.g. mitochondrial or ER stress, can stimulate the expression of FGF21 in several tissues, not only in liver, and consequently alleviate mitochondrial and ER stresses elsewhere in the body. Moreover, the stress-induced FGF21 secretion, e.g. from liver and skeletal muscle, can stimulate the secretion of adiponectin and corticosterone and thus enhance tissue survival in stresses. This resembles a cell non-autonomous regulation of stress resistance and longevity observed in some model organisms. Interestingly, the overexpression of FGF21 is a potent enhancer of longevity in mice, probably by improving healthspan. Given that FGF21 can enhance autophagy and increase mitochondrial respiratory capacity, it facilitates cellular housekeeping and thus increases stress resistance. It is generally recognized that stress resistance enhances lifespan across species. We conclude that FGF21 is a cell non-autonomous enhancer of longevity in mammals.

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FIGURE LEGENDS

Fig. 1. A schematic representation of the signaling pathways which stimulate the expression of FGF21 induced by the integrated stress response (ISR). Stress kinases activate the eIF2 α /ATF4 axis which consequently induces the transcription of the *FGF21* gene through the AARE site. ER stress can also induce the transcription of the *FGF21* gene through the XBP1/ATF6 pathway which targets the ERSE site. The stress kinase-activated ATF4 factor can generate either stress resistance via a number of ISR target genes or cellular apoptosis via CHOP signaling. The activity of eIF2 α can be inhibited by either SIRT1 in energy stresses or negative feedback from ATF4 mediated through GADD34-directed PP1 activation. The activation of eIF2 α is a potent inhibitor of protein synthesis. Abbreviations: AARE, amino acid response element; ATF, activating transcription factor; CHOP, transcription factor C/EBP homologous protein; dsRNA, double-stranded RNA; eIF2 α , eukaryotic translation initiation factor 2 α ; ERSE, ER stress response element; FGF21, fibroblast growth factor 21; GADD34, growth arrest and DNA damage-inducible 34; GCN2, general control non-depressible 2; HRI, heme-regulated eIF2 α kinase; ISR, integrated stress response; PERK, PKR-like endoplasmic reticulum kinase; PKR, protein kinase R; PP1, protein phosphatase 1, SIRT1, sirtuin 1, XBP1, X box-binding protein 1

Fig. 2. FGF21 maintains interorgan homeostasis via systemic regulation in a cell non-autonomous manner. Arrows indicate whether tissue secretes FGF21 into the circulation or it is the direct target of FGF21 signaling. Figure does not show the indirect secondary effects of FGF21 to different tissues.

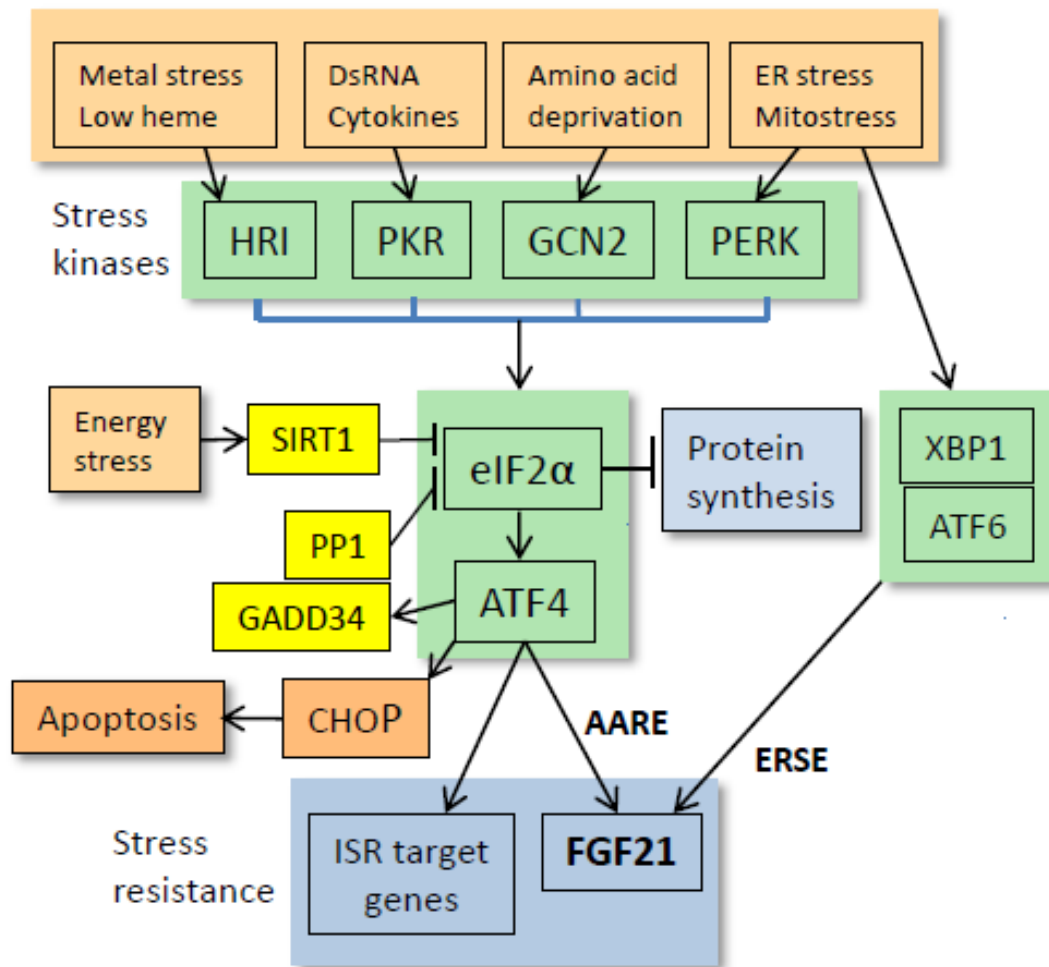


Fig. 1

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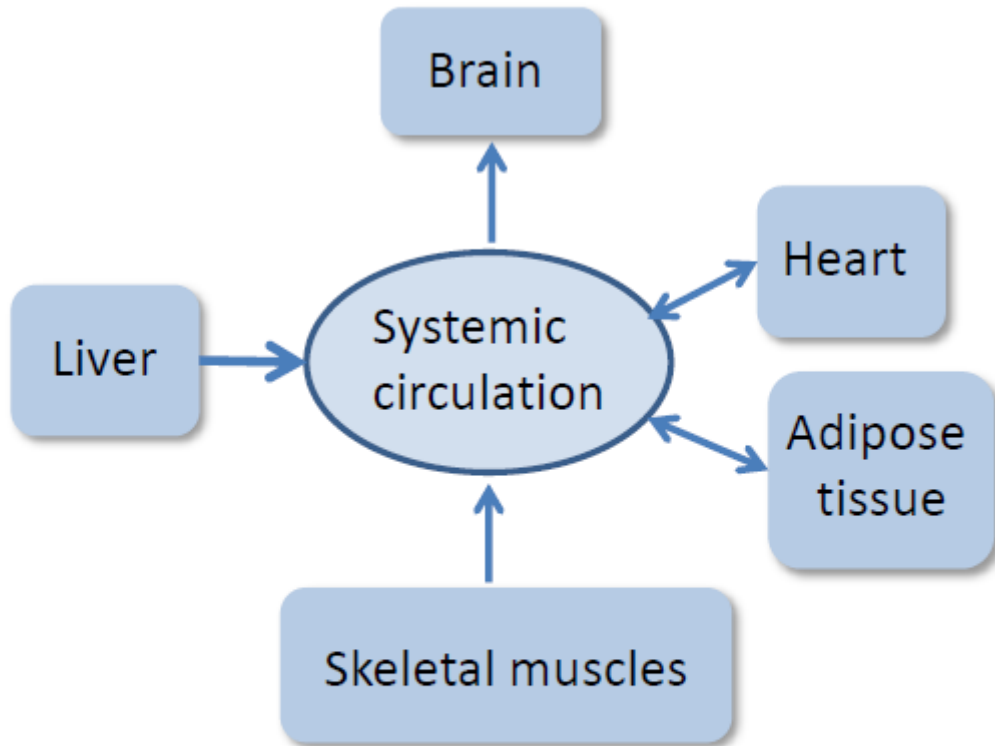


Fig.2

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Highlights

- FGF21 is a multifunctional metabolic and stress hormone
- Stress can induce the expression and secretion of FGF21 from several tissues
- FGF21 is an interorgan regulator which attenuates mitochondrial and ER stresses
- Function of FGF21 resembles a cell non-autonomous regulation in lower animals
- FGF21 is a cell non-autonomous enhancer of longevity in mammals