REVIEW

Regulation of longevity by FGF21: interaction between energy metabolism and stress responses

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Highlights

- FGF21, an endocrine factor, controls energy metabolism and acts as stress hormone
- FGF21 regulates energy metabolism and stress responses via interorgan crosstalk
- FGF21 can increase healthspan and extend lifespan
- FGF21 regulates longevity via e.g. AMPK signaling and somatotropic axis
- FGF21 resistance is encountered in metabolic disorders disrupting healthy aging

ABSTRACT

Fibroblast growth factor 21 (FGF21) is a hormone-like member of FGF family which controls metabolic multiorgan crosstalk enhancing energy expenditure through glucose and lipid metabolism. In addition, FGF21 acts as a stress hormone induced by endoplasmic reticulum stress and dysfunctions of mitochondria and autophagy in several tissues. FGF21 also controls stress responses and metabolism by modulating the functions of somatotropic axis and hypothalamic-pituitary-adrenal (HPA) pathway. FGF21 is a potent longevity factor coordinating interactions between energy metabolism and stress responses. Recent studies have revealed that FGF21 treatment can alleviate many age-related metabolic disorders, e.g. atherosclerosis, obesity, type 2 diabetes, and some cardiovascular diseases. In addition, transgenic mice overexpressing FGF21 have an extended lifespan. However, chronic metabolic and stress-related disorders involving inflammatory responses can provoke FGF21 resistance and thus disturb healthy aging process. First, we will describe the role of FGF21 in interorgan energy metabolism and explain how its functions as a stress hormone can improve healthspan. Next, we will examine both the induction of FGF21 expression via the integrated stress response and the molecular mechanism through which FGF21 enhances healthy aging. Finally, we postulate that FGF21 resistance, similarly to insulin resistance, jeopardizes human healthspan and accelerates the aging process.

Keywords: Ageing, AMPK, FGF21, healthspan, lifespan, miR-34a

1. Introduction

The rate-of-living theory of aging emphasizes the role of metabolic activity in the regulation of longevity, i.e. smaller animals with faster energy metabolism have shorter lifespan than larger animals with slower metabolism (Speakman, 2005; Hulbert et al., 2007). This theory is not completely universal since there are many problems with calculations and there are several exceptions, e.g. animals living in extreme environments. However, many recent studies have revealed compelling evidence that energy metabolism has a fundamental role in the regulation of longevity (Barzilai et al., 2012; Finkel, 2015; Riera and Dillin, 2015). The aging process is associated with a decrease in mitochondrial energy production as well as a decline in many housekeeping and endocrine functions. Recent studies have indicated that mitochondria have a fundamental role in the regulation of the healthy aging process and these organelles have been implicated in the development of many degenerative diseases (Lane et al., 2015; Amigo et al., 2016; Quiros et al., 2016; Sun et al., 2016). Mitochondrial stress as well as endoplasmic reticulum (ER) stress triggers an integrated stress response (ISR) pathway (Pakos-Zebrucka et al., 2016). This mechanism induces adaptive changes to facilitate cellular housekeeping, e.g. it increases autophagy to maintain proteostasis and augments oxidative stress resistance. There is substantial evidence that increased stress resistance can enhance longevity - a phenomenon encountered across species (Longo and Fabrizio, 2002; Zhou et al., 2011; Epel and Lithgow, 2014).

Fibroblast growth factor 21 (FGF21) is a member of the endocrine subfamily of FGFs which in humans contains three peptide hormones, i.e. FGF19, FGF21, and FGF23 (Kuro-o, 2008; Itoh, 2010). FGF21 is not only coordinator of multiorgan energy metabolism (Fisher and Maratos-Flier, 2016) but it is also a stress hormone which can elicit adaptive stress responses, e.g. to combat oxidative stress (Planavila et al., 2015). There is mounting evidence that FGF21 can alleviate many metabolic disorders, such as atherosclerosis, cardiovascular diseases, and metabolic syndrome (Woo et al., 2013; Kim and Lee, 2015; Planavila et al., 2015; Jin et al., 2016). The functions of FGF21 promote the maintenance of healthspan and thus increase life expectancy. Interestingly, there are clear indications that the overexpression of FGF21 can protect against age-related changes, e.g. delay thymic involution

(Youm et al., 2016), and even extend the lifespan of mice (Inagaki et al., 2008; Zhang et al., 2012). Recent studies have revealed several molecular mechanisms through which FGF21 signaling can enhance healthy aging (Section 4.) For instance, FGF21 stimulates AMPK signaling and thus it can control not only energy metabolism but also activate autophagy and inhibit inflammation. FGF21 can also modulate the activity of many hormonal systems, e.g. the somatotropic axis and hypothalamic-pituitary-adrenal (HPA) pathway. We will first review the observations that FGF21 has a crucial role in the regulation of healthspan and lifespan. Next, we will describe in detail the molecular mechanisms which reveal how FGF21 can regulate longevity through its ability to promote interactions between energy metabolism and stress responses. Finally, we will emphasize that chronic metabolic and stress-related disorders provoke FGF21 resistance which might jeopardize the healthy aging process.

2. Functional properties of FGF21

The FGF gene family has been largely conserved throughout metazoan evolution (Itoh and Ornitz, 2004; Murata et al., 2011). The *FGF21* gene seems to have been generated via genome duplication events and it appeared even in the teleosts in the vertebrate lineage. Nishimura et al. (2000) cloned both the mouse and human *FGF21* genes which were robustly expressed in liver and at a lower level in thymus. Subsequent studies have revealed that the expression of FGF21 can also be induced by different stresses in adipose tissue (Muise et al., 2008) as well as in skeletal (Keipert et al., 2014) and cardiac (Brahma et al., 2014) muscles. The FGF21 peptide hormone is mainly secreted from liver under normal conditions (Markan et al., 2014) and consequently it targets via systemic circulation the FGF receptor 1 (FGFR1) and FGFR3 (Suzuki et al., 2008). Those FGFRs assemble a specific receptor complex with the β-klotho protein and subsequently they activate several downstream signaling pathways, e.g. AMPK, MAPK/ERK, and PI3K-AKT pathways (Chau et al., 2010; Patel et al., 2014; Zhang et al., 2015). It should be emphasized that FGF21 controls the downstream signaling pathways in both a tissue-specific and a context-dependent manner, e.g. regulating the metabolic functions of peripheral tissues (Woo et al., 2013; Fisher and Maratos-Flier, 2016). FGF21 is an endocrine messenger which can also induce hormonal responses in other tissues,

e.g. the secretion of adiponectin from adipose tissues (Section 4.4.) and corticotropin-releasing hormone (CRH) from hypothalamus (Section 2.2.). FGF21 is also able to modulate the signaling mechanisms of some hormones, e.g. growth hormone (GH) (Section 4.3.) and insulin (Camporez et al., 2013) in their target tissues. Moreover, endocrine FGF21 can stimulate the secretion of digestive enzymes from the pancreatic acinar cells and thus enhance the digestion of food in stomach (Coate et al., 2017). This kind of multiorgan crosstalk improves the capacity of FGF21 to regulate energy metabolic homeostasis and to respond promptly to different stresses.

2.1. FGF21 controls energy metabolism

FGF21 has a fundamental role in the regulation of systemic energy metabolism, especially glucose and lipid metabolism. Recently, this topic has been extensively discussed in several review articles (Woo et al., 2013; Kharitonenkov and DiMarchi, 2015; Fisher and Maratos-Flier, 2016). FGF21 enhances glucose metabolism by increasing glucose uptake into tissues, e.g. by increasing insulin sensitivity, and thus it decreases serum hyperglycemia. FGF21 also reduces hepatic gluconeogenesis, e.g. a lack of FGF21 in mice evokes insulin resistance and promotes gluconeogenesis and glucose production by liver (Wang et al., 2014; Camporez et al., 2015). FGF21 increases free fatty acid (FFA) oxidation in tissues and inhibits lipogenesis in liver; consequently there is a decline in the levels of FFA and LDL-cholesterol in the circulation (Woo et al., 2013). Emanuelli et al. (2014) demonstrated in LIRKO mice (liver-specific insulin receptor knockout mice) that there is a significant crosstalk between insulin and FGF21 in the regulation of systemic metabolism. For instance, FGF21 treatment normalized the hyperglycemia of LIRKO mice by increasing glucose uptake and expenditure in brown adipose tissue. It is clear that FGF21 increases energy metabolic activity and energy expenditure in a manner that benefits organisms when they encounter stresses, e.g. starvation/dietary restriction, but it also protects against hepatic steatosis (Xu et al., 2009) and atherosclerosis (Jin et al., 2016). Peroxisome proliferator-activated receptor α (PPARα) is a key transcription factor which activates the expression of FGF21 in liver (Badman et al., 2007; Lundasen et al., 2007). Recently, Vernia et al. (2014 and 2016) demonstrated that c-Jun NH2-terminal kinase

(JNK) repressed the function of PPARα-FGF21 axis in mouse liver. They observed that the deficiency of hepatic JNK activity increased the expression of FGF21 and consequently reduced the diet-induced obesity and improved insulin sensitivity. It is previously known that JNK activity has an important role in the control of mammalian obesity and insulin resistance (Hirosumi et al., 2002). Given that FGF21 has a capacity to normalize glucose and lipid metabolism and maintain energy homeostasis, it has become a focus of intense research, especially the search for therapeutic applications to alleviate metabolic disorders (Zhang and Li, 2014). For instance, FGF21 mimetics and antibody-mediated activation of FGFR1 have been evaluated in the therapy of metabolic disorders (Wu et al., 2011; Gimeno and Moller, 2014). The therapeutic activation of FGF21 signaling is a promising treatment not only for metabolic disorders but also to alleviate stress-related conditions, such as cardiac hypertrophy (Planavila et al., 2013) and ischemia (Liu et al., 2013).

There is compelling evidence indicating that both nutritional and cellular stresses can stimulate the expression of FGF21 in liver and some other responsive tissues, leading to an increase in the level of FGF21 in the circulation (Fig. 1). Inagaki et al. (2007) detected a 28-fold increase in the expression of FGF21 in mouse liver after only a 12h fasting period. The upregulation of FGF21 in liver was induced by PPARα transcription factor. The fasting-induced increase in FGF21 expression stimulated ketogenesis in liver and promoted lipolysis in white adipose tissue. Fasting also generated torpor, a hibernation-like state, especially in FGF21-overexpressing transgenic mice (Inagaki et al., 2007). Fazeli et al. (2015) revealed that fasting strongly increased the level of serum FGF21 within hours in mice, whereas in humans, the upregulation did not appear until there had been 7-10 days of fasting. Moreover, provision of a methionine-restricted diet (Lees et al., 2014) or a protein-low diet (Laeger et al., 2014) increased the level of serum FGF21 in mice (Fig. 1). The effects of nutritional overload, such as when animals are fed a high-fat diet, are more complex with respect to the metabolic regulation by FGF21. It is known that a high-fat diet commonly increases the expression of FGF21 in liver and white adipose tissues as well as elevates the level of FGF21 in blood (Sun et al., 2012; Nygaard et al., 2014). Sun et al. (2012) observed that a long-term high-fat diet increased the expression levels of FGF21, β-klotho, FGFR1, and FGFR3 in both liver and adipose tissue in $ApoE^{-/-}$

mice. Given that FGF21 enhances FFA oxidation in tissues and decreases the levels of FFA and LDL-cholesterol in the circulation, it is puzzling that there is a clear increase in the level of serum FGF21 in obese mice and humans (Zhang et al., 2008; Fisher et al., 2010). However, it might be the amount of fat present in liver rather than overall adiposity which induces the increase in the level of serum FGF21 (Tyynismaa et al., 2011). Moreover, acute aerobic exercise, known to boost the circulating level of FGF21 (Fig. 1), caused a smaller increase in the level of serum FGF21 in obese individuals compared to normal-weight persons (Slusher et al., 2015). Currently, there is substantial evidence indicating that obesity is an FGF21-resistant state (Fisher et al., 2010), as a result of an impaired FGF21 signaling (Section 5.). This means that an increased level of serum FGF21 does not indicate whether FGF21 can enhance energy metabolism in tissues.

2.2. FGF21 acts as a stress hormone

FGF21 has crucial functions as a stress hormone in the maintenance of tissue homeostasis in the organism (Kim and Lee, 2015). FGF21 can act in an autocrine and paracrine fashion within tissues or through systemic regulation between multiple tissues. FGF21 can also control the secretion of other hormones, e.g. adiponectin, catecholamines, and glucocorticoids, and thus generate adaptive responses to restore homeostasis. There is compelling evidence that ER stress can induce the expression of FGF21 and increase its level not only in the circulation but also in liver (Schaap et al., 2013; Jiang et al., 2014; Kim et al., 2015), adipocytes, and cardiac and skeletal muscles (Brahma et al., 2014; Wan et al., 2014; Miyake et al., 2016) (Fig. 1). It seems that the transactivation of the *FGF21* gene is involved in the unfolded protein response (UPR) induced by ER stress (erUPR). There are many studies indicating that the erUPR stimulates the expression of FGF21 through the PERK-eIF2α-ATF4 axis (Section 4.1.). This pathway is one of the integrated stress response pathways (Pakos-Zebrucka et al., 2016) e.g. controlling energy metabolism and cellular recovery (Baird and Wek, 2012; Pakos-Zebrucka et al., 2016) and it might also extend lifespan (Li et al., 2014). Jiang et al. (2014) demonstrated that another branch of ER stress signaling, i.e. the IRE1α-XBP1 axis, was also able to stimulate the activation of *FGF21* gene in mouse primary hepatocytes. Interestingly, Dong et al.

(2015) revealed that ER stress increased the expression of hepatic β-klotho protein, thus enhancing the efficiency of FGF21-induced signaling in liver. There are studies indicating that FGF21 might mediate a negative feedback against ER stress. For instance, Jiang et al. (2014) reported that FGF21 exposure alleviated the hepatic steatosis induced by ER stress. Other studies have revealed that in mice FGF21 administration ameliorated the ER stress-induced atherosclerosis (Wu et al., 2015) and reduced metabolic stress in the liver of obese mice (Kim et al., 2015). These studies clearly imply that FGF21 expression and secretion can protect tissues against the detrimental effects induced by ER stress, probably in a cell non-autonomous manner within tissues. Given that ER stress is associated with the aging process (Salminen and Kaarniranta, 2010a), it seems likely that an enhanced expression of FGF21 could prevent age-related tissue degeneration (Section 3).

Mitochondria are sensitive sensors of cellular stress; these subcellular organelles can trigger stress responses via the mitochondrial unfolded protein response (mtUPR) (Yun and Finkel, 2014; Quiros et al., 2016; Sun et al., 2016). Recent studies have revealed that mtUPR can regulate chromatin reorganization and thus promote longevity (Tian et al., 2016). In 2010, Tyynismaa et al. demonstrated that an experimental mouse model (the Deletor mouse) involving an increased accumulation of mitochondrial DNA deletions and deficits in respiratory capacity induced a threefold increase in the expression of FGF21 in mouse skeletal muscle. Consequently, Suomalainen et al. (2011) observed that an increased level of serum FGF21 was a feasible diagnostic biomarker for deficiencies in mitochondrial respiration in skeletal muscles. The molecular mechanisms of FGF21 induction caused by mitochondrial disturbances still need to be clarified. There are some observations that the disruption of mitochondrial fission by deleting the fission inducer DRP1 in mouse liver could stimulate the expression of FGF21 (Wang et al., 2015a). A lack of cellular autophagy impairing mitophagy also stimulated the expression of FGF21 and increased its level in the circulation (Kim et al., 2013b; Yasuda-Yamahara et al., 2015). Surprisingly, disturbances of mitochondrial fission and mitophagy prevented diet-induced obesity and insulin resistance, most likely this was attributable to an increased level of serum FGF21. Keipert et al. (2014) demonstrated that the overexpression of mitochondrial uncoupling protein 1 (UCP1) in the skeletal muscles of transgenic mice induced a

fivefold increase in the level of circulating FGF21. It is known that the uncoupling of mitochondrial respiration can improve whole-body energy metabolism and reduce the risk for age-related diseases, e.g. atherosclerosis, type 2 diabetes and obesity (Gates et al., 2007; Neschen et al., 2008); one could speculate that these effects were mediated by increased level of circulating FGF21. It seems that there is a feedback loop in the regulation of FGF21 since an increased expression of FGF21 was able to improve mitochondrial function by increasing the expression and activity of PGC-1α, a major transcription factor of mitochondrial biogenesis and energy metabolism (Potthoff et al., 2009; Mäkelä et al., 2014; Ji et al., 2015). FGF21 signaling, both auto/paracrine and endocrine, requires an active FGFR1/β-klotho complex and for instance, several studies have revealed that the expression of β-klotho protein is very low or negligible in mammalian skeletal muscles (Ogawa et al., 2007; Keipert et al., 2014). Corroborating this observation, Ost et al. (2015) demonstrated that the muscle metabolic rescue process associated with mitochondrial stress was independent from the auto/paracrine regulation of muscle-derived FGF21. However, Vandanmagsar et al. (2016) revealed that FGF21 secretion from muscles caused by the deficiency of mitochondrial fatty acid oxidation increased glucose uptake into muscles through the paracrine action of FGF21. Moreover, it seems that the muscle-derived FGF21 does not affect the systemic metabolic regulation (Ost et al., 2015; Vandanmagsar et al., 2016). Currently, it needs to be clarified whether the muscle stress-related FGF21 secretion have any effect on cell non-autonomous metabolic regulation.

Recent studies have revealed that circulating FGF21 can also target the hypothalamus and thus activate stress reactions induced by the HPA axis (Bookout et al., 2013; Liang et al., 2014; Patel et al., 2015; Sa-Nguanmoo et al., 2016). It is known that FGF21 can penetrate into brain from the bloodstream (Hsuchou et al., 2007) and moreover, both FGFR1 and its co-receptor β-klotho are expressed in distinct nuclei in the hypothalamus (Bookout et al., 2013; Liang et al., 2014; Sa-Nguanmoo et al., 2016). In 2014, Liang et al. demonstrated that systemic FGF21 administration stimulated the production of CRH by activating ERK1/2-CREB signaling in the hypothalamic paraventricular nucleus (PVN). Consequently, CRH stimulated the HPA axis and triggered the secretion of corticosterone from adrenal cortex (Liang et al., 2014). Corticosterone increases blood

glucose level and enhances hepatic gluconeogenesis. Bookout et al. (2013) also demonstrated that an elevation in the systemic level of FGF21 could increase the concentration of serum corticosterone via the hypothalamic suprachiasmatic nucleus (SCN) in a β-klotho-dependent manner. They also emphasized that circulating FGF21 regulated circadian rhythm through the SCN, a well-known circadian pacemaker. Subsequently, Patel et al. (2015) revealed that an increased corticosterone level induced the expression of FGF21 in mouse liver. They reported that the expression of FGF21 was stimulated through the binding of activated glucocorticoid receptor (GR) to the non-canonical GR binding element in the promoter of the *FGF21* gene. These results convincingly showed that there is a FGF21-mediated feed-forward loop triggering cortisol production in stress conditions. Owen et al. (2014) demonstrated that the administration of FGF21 increased the expression of hypothalamic CRH in mice and consequently increased the level of adrenocorticotropic hormone (ACTH) in blood indicating the activation of HPA axis. They also reported that FGF21 evoked an increase in sympathetic nerve activity to brown adipose tissue. This sympathetic activity could be inhibited by antagonism of adrenergic receptors (Douris et al., 2015). It is well known that catecholamines are another hormonal system activated by stress (Kvetnansky et al., 2009). Recently, Zhao et al. (2015) demonstrated that the injection of FGF21 increased the serum concentrations of both epinephrine and norepinephrine in FGF21 knockout mice. Given that FGF21 stimulates the HPA axis, it is interesting that FGF21 not only controls energy metabolism via the crosstalk between peripheral tissues but it can also stimulate the neural circuitry to adapt organism to stress thus controlling e.g. energy metabolism, immune system, and some other survival mechanisms.

3. FGF21 regulates healthspan and lifespan

Since FGF21 regulates the interaction between energy metabolism and stress responses, it was obviously interesting to determine whether the overexpression of FGF21 in transgenic mice would extend their lifespan. In 2007, Inagaki et al. generated a transgenic mouse overexpressing FGF21 (tg-FGF21) under the control of the ApoE promoter. The tg-FGF21 mice displayed a 5-fold higher plasma concentration of FGF21 than observed in even the fasted wild-type mice. Fasting did not further

increase the FGF21 level in the tg-FGF21 mice (Inagaki et al., 2008). Both male and female tg-FGF21 mice were smaller than their wild-type littermates. Interestingly, the lifespan of tg-FGF21 mice was significantly extended as compared to that of their wild-type counterparts (Zhang et al., 2012). There was a 36% increase in the median survival time for tg-FGF21 mice although the longevity was to some extent more evident in the transgenic females. Subsequently, the tg-FGF21 mice have been thoroughly characterized in order to reveal the potential cause for the extension of their lifespan (Inagaki et al., 2008; Zhang et al., 2012). The screening of circulatory factors revealed that the serum levels of insulin and insulin-like growth factor-1 (IGF-1) were considerably decreased in the tg-FGF21 mice. The expression of IGF-1 also was significantly reduced in the liver of tg-FGF21 mice. Given that the circulating level of growth hormone (GH) was strongly increased in the tg-FGF21 mice, this indicated that the tg-FGF21 mice were GH resistant (Inagaki et al., 2008). It is known that GH deficient dwarf mice live longer than their wild-type counterparts (Section 4.3.). Moreover, the serum level of adiponectin was increased in the tg-FGF21 mice and accordingly the serum concentrations of glucose and triglycerides were lower in these mice (Zhang et al., 2012). These changes clearly indicated that an increased FGF21 level affected the energy metabolism of the whole organism by re-setting the hormonal balance. There are also studies indicating that FGF21 exposure can prevent an accelerated aging process in brain e.g. as induced by angiotensin II (Ang II) (Wang et al., 2016b) or D-galactose (Yu et al., 2015a). It seems that the anti-aging effects against these inducers are based on the capacity of FGF21 to alleviate the effects of excessive oxidative stress. FGF21 could also prevent the premature cerebrovascular aging induced by Ang II since FGF21 exposure activated AMPK signaling which then stimulated mitochondrial biogenesis and inhibited p53 function (Wang et al., 2016b). In addition, the age-related thymic involution was clearly delayed in the tg-FGF21 mice (Youm et al., 2016). The lack of thymic degeneration was attributed to a decrease in lipid accumulation into thymus which subsequently postponed the appearance of immune senescence in the tg-FGF21 mice (Section 4.5.).

Given that dietary restriction is a potent inducer of FGF21 expression, FGF21 has been called a dietary restriction mimetic (Mendelsohn and Larrick, 2012). For instance, FGF21 can increase adipose

tissue lipolysis, enhance liver ketogenesis, and improve mitochondrial respiration (Potthoff et al., 2009; Kuhla et al., 2014; Liang et al., 2014). The gene expression profiling of the liver revealed a distinct overlap in the altered patterns of gene expression observed between caloric restricted and the tg-FGF21 mice (Zhang et al., 2012). It is known well that dietary restriction is the most fundamental way to extend lifespan across metazoan species (Canto and Auwerx, 2009; Fontana et al., 2010; Swindell, 2012). However, it is not simply caloric restriction which increases lifespan since a low-protein high-carbohydrate (Le Couteur et al., 2016) and a methionine-restricted (Orentreich et al., 1993; Perrone et al., 2013) diets can also extend lifespan. Interestingly, both the protein deficient diet (Laeger et al., 2014) and the methionine-restricted diet (Lees et al., 2014) also increased the serum level of FGF21 in mice. Lees et al. (2014) demonstrated that a methionine-low diet was able to reverse many age-related alterations, e.g. obesity and insulin resistance, in adult mice. Gender-specific differences might also appear in the responses of FGF21 to dietary restriction diets. Lee et al. (2016) reported that a methionine-choline deficient diet induced a more robust increase of FGF21 levels in liver and serum in female mice compared to those of male mice. There is mounting evidence that different food restriction diets, both caloric, protein, and distinct amino acid diets, can improve metabolic profiles and consequently prevent many age-associated diseases, thus promoting the healthspan in a wide range of species from rodents to humans (Omodei and Fontana, 2011; Mattison et al., 2012; Perrone et al., 2013; Mirzaei et al., 2014). It seems that FGF21 has a key role in these processes, and thus caloric restriction mimetics and modified diets have a great potential to enhance healthy aging (Ingram and Roth, 2015).

Many long-lived mutants, either those of *Caenorhabditis elegans* or long-living mice, have been revealed to carry mitochondrial protein defects (Liu et al., 2005; Pulliam et al., 2013; Munkacsy and Rea, 2014). For instance, the deficiency of the *clk-1/mclk1* gene increased stress resistance and extended lifespan in both *C. elegans* and transgenic mice (Liu et al., 2005; Takahashi et al., 2014). Currently, it is not known whether that mutation was linked to an increased expression of FGF21 although it is likely that mitochondrial disturbances could induce the expression of FGF21 (Section 2.2.). There are observations that the *INDY* mutation protected transgenic mice against insulin

resistance and obesity through the activation of AMPK (Birkenfeld et al., 2011), which is a well-known target of FGF21 signaling (Salminen et al., 2017). Moreover, mitochondrial uncoupling with UCP proteins can extend the lifespan by combatting against excessive ROS production (Mookerjee et al., 2010). The overexpression of UCP1 in mouse skeletal muscle increased the expression of FGF21 and improved the metabolic phenotype of tg-UCP1 mice (Keipert et al., 2014; Kwon et al., 2015). However, excessive mitochondrial defects in the mtDNA mutator mice induced a progeroid state although the expression of FGF21 was increased and mice were resistant against the obesity induced by a high-fat diet (Wall et al., 2015). It seems that an increased expression of FGF21 is not able to prevent the aging process induced by extreme mitochondrial stress, e.g. in the case of mtDNA mutator mice.

White adipose tissue (WAT) and brown adipose tissue (BAT) are the major adipose tissues in the body. It is known that FGF21 stimulates the secretion of adiponectin from both WAT and BAT. We will discuss more thoroughly the effects of adiponectin in the maintenance of healthspan in Section 4.4. BAT is specialized on thermogenesis and thus the regulation of energy expenditure in body (Harms and Seale, 2013; Bartelt and Heeren, 2014). Cold-exposure and β-adrenergic stimulation can induce the transdifferentiation of WAT to BAT, an adipose type rich of mitochondria. Fisher et al. (2012) demonstrated that FGF21 was involved in the browning process since it increased the activity of PGC-1α and the expression of UCP1 through the autocrine/paracrine signaling in WAT. Hondares et al. (2011) reported that norepinephrine, stimulated by cold-exposure, increased FGF21 expression in BAT and elevated the level of serum FGF21 in mice. BAT is a secretory organ releasing many adipokines which subsequently regulate systemic metabolism (Villarroya et al., 2017). There is compelling evidence that the browning of WAT and the function of BAT are impaired during the aging process (Lecoultre and Ravussin, 2011; Graja and Schulz, 2014). The loss of BAT activity disturbs the capacity of body to control energy expenditure and probably enhances the age-related obesity. Recently, Darcy et al. (2016) revealed that the function of BAT was substantially improved in long-lived Ames dwarf mice compared to normal counterparts. Recent studies with PET imaging techniques have revealed that adult humans possess metabolically active BAT, which is reduced in obese patients and its amount declines with aging (Lecoultre and Ravussin, 2011; Giralt et al., 2015).

Currently, the role of FGF21 resistance in the dysfunction of BAT with aging and obesity needs to be clarified.

It is known that the stimulation of FGF21 signaling can prevent several common diseases and thus reduce untimely mortality (see above). However, there are also less positive studies which indicated that the chronic administration of FGF21 can induce pathological changes in bones and cause skeletal fragility (Wei et al., 2012; Wang et al., 2015c). Furthermore, tg-FGF21 mice also displayed a significant loss of total bone mass (Wei et al., 2012; Zhang et al., 2012). Wei et al. (2012) demonstrated that FGF21 inhibited osteoblastogenesis and thus reduced bone formation and simultaneously bone resorption was also increased. Interestingly, they observed that FGF21 stimulated the differentiation of bone marrow cells into adipocytes rather than osteoblasts; the adipogenesis was mediated through the activation of PPAR-γ in bone marrow as well as in adipose tissue. They also reported that the deletion of FGF21 conferred a tolerance to the bone deficit induced by rosiglitazone, an agonist to PPAR-γ signaling. Moreover, Wang et al. (2015c) demonstrated that FGF21 stimulated the hepatic expression of IGF-binding protein 1 (IGFBP1) which consequently enhanced osteoclastogenesis and provoked bone resorption. In addition, there are reports indicating that FGF21 reduced growth and stature by inhibiting the GH sensitivity of the chondrocytes present in the growth plate (Wu et al., 2012). This mechanism is consistent with the observations that food deprivation has harmful effects on the growth of children. These studies emphasize that the planning of FGF21 therapies for metabolic diseases will need to pay attention to bone resorption.

4. Molecular mechanisms of FGF21-enhanced longevity

4.1. FGF21 expression is stimulated by eIF2α-ATF4 stress response pathway

FGF21 is an important regulator of stress responses via the crosstalk between different tissues (Section 2.2.). Interestingly, there is mounting evidence that the activation of the *FGF21* gene is a target of the integrated stress response (ISR) pathway (De Sousa-Coelho et al., 2012; Schaap et al., 2013; Keipert et al., 2014; Wan et al., 2014; Laeger et al., 2016). The ISR is a common stress response mechanism mediating the activation of the eukaryotic initiation factor 2α (eIF2α)-activating

transcription factor 4 (ATF4) signaling pathway which can be stimulated by different cellular stresses, e.g. ER stress, mitochondrial stress, and amino acid deprivation (Pakos-Zebrucka et al., 2016) (Fig. 2). The eIF2α kinase can be activated through the phosphorylation by upstream kinases, e.g. GCN2 which is stimulated by amino acid deprivation or PERK, a protein kinase activated by ER stress and also mitochondrial stress. The phosphorylation of eIF2α on Ser51 activates the ATF4 transcription factor, which in the presence of distinct cofactors, induces the expression of several survival genes including autophagy genes (Rzymski et al., 2010; B'chir et al., 2013; Pike et al., 2013).

De Sousa-Coelho et al. (2012) reported that the expression of FGF21 was induced by amino acid deficiency in human HepG2 cells as well as in leucine-deprived mouse liver. They observed that the transcription of *FGF21* gene was activated by ATF4 after its binding to two amino acid-response elements (AARE) in the promoter of the *FGF21* gene. Laeger et al. (2016) reported that feeding mice a protein restriction diet induced the expression of FGF21 through the activation of GCN2 kinase in acute treatments but not during chronic protein deprivation. Recently, Maida et al. (2016) reported that the diet containing a reduced level of nonessential amino acids (NEAA) increased the expression of FGF21 in mouse liver and consequently improved metabolic health in obesity. The NEAA diet stimulated hepatic ISR that increased the expression and secretion of FGF21 through the induction of nuclear protein 1 (NUPR1). It seems that the depletion of glutamine can also trigger the expression of hepatic FGF21. Cornu et al. (2014) demonstrated that the activation of hepatic mTORC1 by knocking out its repressor *Tsc1* gene reduced the hepatic and plasma levels of glutamine and subsequently stimulated FGF21 expression in mouse liver (Fig. 2). They reported that the ectopic activation of mTORC1 induced the expression of FGF21 through the PGC-1α-dependent pathway. Increased secretion of FGF21 affected mouse systemic physiology, e.g. it reduced locomotor activity and body temperature. Recently, Guridi et al. (2015) demonstrated that the skeletal muscle-specific activation of mTORC1 by knocking out TSC1 stimulated the expression and secretion of FGF21. They revealed that the ectopic activation of mTORC1 in skeletal muscles triggered ER stress which promoted the expression of FGF21 via the PERK/eIF2α/ATF4 pathway. It seems that mTORC1 activity can increase the expression of FGF21 through different pathways in liver and skeletal muscles. Schaap et

al. (2013) demonstrated that ER stress induced the ATF4-facilitated transcription of *FGF21* gene in cultured hepatoma and kidney cells as well as in mouse liver. They observed that the ER stress-induced FGF21 transcription was mediated through the PERK/eIF2α/ATF4 pathway via the AARE element in the promoter of *FGF21* gene. These studies clearly indicated that protein restriction and ER stress stimulated the expression of FGF21 through different upstream signaling pathways although the activated ATF4 was targeted to the same AARE elements in the *FGF21* promoter. In addition, Miyake et al. (2016) reported that the tissue-specific expression of active PERK in mouse skeletal muscle induced the eIF2α/ATF4-driven FGF21 expression and its subsequent secretion.

As described above (Section 2.2.), mitochondrial stress is a potent stimulator of the expression and secretion of FGF21 in many tissues. Keipert et al. (2014) observed that the ISR pathway, i.e. the activation of eIF2α-ATF4 signaling, was robustly stimulated in the skeletal muscles of tg-UCP1 mice. The induction of FGF21 expression and its secretion were associated with reduced mitochondrial respiration. It is known that the inhibitors of mitochondrial respiratory chain can induce the expression of FGF21 through the activation of ATF4 (Kim et al., 2013a; Keipert et al., 2014). Kim et al. (2013a) reported that metformin, an activator of AMPK, inhibited the activity of mitochondrial complex I in an AMPK-independent manner and enhanced the expression of FGF21 in several cell lines. This response was mediated through the PERK-eIF2α-ATF4 axis, i.e. the same pathway as known to be involved in ER stress. They also observed that metformin stimulated the ATF-dependent induction of FGF21 in mouse liver. Moreover, in human diabetic patients, metformin therapy increased the serum level of FGF21. These results indicate that some of the beneficial metabolic effects of metformin may be mediated by FGF21. There seems to be a complex crosstalk between ER stress and mitochondrial stress responses (Senft and Ronai, 2015), and thus the activation mechanisms of ISR in mitochondrial stress need to be clarified. Oxidative stress and ROS generation could be the common denominator since mitochondria are the main source of ROS production. There are reports indicating that ROS can activate the PERK-mediated ISR pathway (Liu et al., 2008; Verfaillie et al., 2012) although in some contexts, mitochondrial ROS production stimulated the GCN2-dependent activation of eIF2α-ATF4 axis (Wang et al., 2016a) (Fig. 2). Liu et al. (2008) demonstrated that hypoxic ROS production

promoted the PERK-eIF2α signaling and consequently eIF2α activated not only ATF4 but in addition, eIF2α directly inhibited protein translation, commonly observed in hypoxic conditions as well as in the aging process. Currently, it is not known whether ROS stimulates the expression of FGF21 via the ISR. However, it is recognized that FGF21 is a potent inhibitor of oxidative stress since it stimulates the expression of antioxidant enzymes and thus protects against oxidative stress (Planavila et al., 2015; Yu et al., 2015a).

4.2. FGF21 activates AMPK-mediated pro-longevity regulation

FGF21 is a multiorgan energy and stress regulator which can control many downstream signaling pathways in a tissue-dependent manner. The metabolic responses induced by FGF21 and AMPK activation are very similar in the regulation of both glucose and lipid metabolism, which implies that FGF21 might control energy metabolism through the AMPK signaling (Salminen et al., 2017) (Section 2.1.). There is also mounting evidence that the maintenance of efficient AMPK signaling can increase not only healthspan but also extend lifespan (Curtis et al., 2006; Mair et al., 2011; Salminen and Kaarniranta, 2012; Burkewitz et al., 2014). In their seminal study, Chau et al. (2010) demonstrated that FGF21 activated AMPK signaling in cultured adipocytes and mouse adipose tissues. They reported that FGF21 activated AMPK signaling through LKB1, an upstream kinase of AMPK. Subsequently, AMPK stimulated SIRT1 and PGC-1α, a key regulator of mitochondrial metabolism. FGF21 can stimulate AMPK signaling either directly through the FGFR1/klotho-β complex or indirectly by inducing the expression of adiponectin and corticosteroids (Salminen et al., 2017). Lin et al. (2013) reported that FGF21 increased the expression and secretion of adiponectin from mouse adipocytes. It is known that adiponectin can stimulate AMPK signaling in several tissues, e.g. liver, hypothalamus, and cardiac and skeletal muscles (Yamauchi et al., 2002; Lim et al., 2010). Adiponectin has important functions in energy metabolism and thus it can improve healthspan (Section 4.4.). In addition, as described above (Section 2.2.), FGF21 can stimulate the HPA axis and increase the secretion of corticosteroids from adrenal cortex. There are several studies indicating that corticosteroids, especially the potent analog dexamethasone, can control AMPK signaling, either

enhancing or suppressing its activation, in a tissue-dependent manner (Christ-Crain et al., 2008; Zhao et al., 2008; Scerif et al., 2013). The activation of HPA cascades by FGF21 might have an important role in ER stress and mitochondrial dysfunctions, e.g. in the control of metabolism under stresses. One should not forget that the HPA hormones stimulated by FGF21 have also many AMPK-independent responses in the body.

AMPK signaling is linked to several downstream pathways which are associated with the control of the aging process, e.g. SIRT1, mTORC1, and NF-κB signaling (Fig. 2.). AMPK activation is a potent inducer of autophagy by activating the ULK1 and SIRT1 pathways and inhibiting mTORC1 signaling (Lee et al., 2008; Canto et al., 2009; Mihaylova and Shaw, 2011; Salminen and Kaarniranta, 2012). Currently, there are only a few studies demonstrating that FGF21 can stimulate autophagy, either directly or through adiponectin secretion (Liu et al., 2015b; Zhang et al., 2016; Zhu et al., 2016). For instance, Zhu et al. (2016) demonstrated that FGF21 administration improved insulin sensitivity and ameliorated hepatic steatosis in obese mouse model. They observed that FGF21 increased AMPK activity and improved autophagic flux in liver by stimulating the expression of autophagy genes. FGF21 also stimulates the secretion of adiponectin from adipose tissues and consequently it can promote autophagy in target tissues (Section 4.4.). The autophagic capabilities of tissues decline with aging which disturbs their ability to maintain proteostasis, thus enhancing the aging process (Cuervo et al., 2008; Salminen and Kaarniranta, 2009; Rubinsztein et al., 2011). It needs to be clarified whether the FGF21-induced extension of lifespan is attributed to an increased activity of autophagy, especially during dietary restriction. In conjunction with autophagy, the FGF21/AMPK signaling can stimulate the efflux of cholesterol from macrophages, macrophage-derived foam cells, and endothelial cells, and thus it can prevent atherosclerosis and promote vascular health (Li et al., 2010a,b; Lin et al., 2014; Shang et al., 2015). Many studies have revealed that AMPK signaling can activate cholesterol efflux by increasing the expression of the ATP-binding cassette transporters, e.g. ABCA1 and ABCG1 (Li et al., 2010a,b; Lin et al., 2015; Kemmerer et al., 2016). Recently, Lin et al. (2014) and Shang et al. (2015) demonstrated that FGF21 increased the efflux of cholesterol from macrophage-derived foam cells by enhancing the expression of ABCA1 and ABCG1 transporters.

They also reported that the transcription of the *ABCA1* gene was induced by liver X receptor α (LXRα) transcription factor. These studies clearly revealed that the FGF21/AMPK axis can stimulate cholesterol efflux and thus counteract age-related vascular diseases.

There is convincing evidence that FGF21 regulates mitochondrial biogenesis and oxidative metabolism by activating PGC-1α through the FGF21-AMPK-SIRT1 pathway (Chau et al., 2010). Chau et al. (2010) reported that FGF21 increased the expression of mitochondrial proteins and potentiated mitochondrial respiration in mouse and human adipocytes. FGF21 also stimulated the expression of PGC-1α in mouse liver (Potthoff et al., 2009) and human dopaminergic neurons (Mäkelä et al., 2014). Potthoff et al. (2009) demonstrated that the fasting-induced expression of FGF21 increased the expression of hepatic PGC-1α and consequently stimulated fatty acid oxidation and Krebs cycle flux in mouse liver. It is known that the activation of PGC-1α and the improved mitochondrial functions have a crucial role in the prevention of age-related diseases (Wenz, 2011; Austin and St-Pierre, 2012). In addition to PGC-1α, the AMPK-SIRT1 axis has connections to several other aging-linked targets, e.g. FOXO, p53, HIF1α, and NF-κB (Houtkooper et al., 2012; Nogueiras et al., 2012), and thus they are also potential downstream pathways for regulating FGF21-AMPK-SIRT1 signaling. Recently, Fujita et al. (2016) reported that DEC1 (differentiated embryo chondrocyte 1) is a potent inhibitor of FGF21 signaling in mouse liver. It is known that DEC1 transcription factor can suppress AMPK signaling by inhibiting the expression of LKB1, an upstream kinase of AMPK (Sato et al., 2015). Qian et al. (2008) demonstrated that *DEC1* is a target gene of p53 and is able to mediate the p53-dependent premature cellular senescence. Interestingly, Wang et al. (2016b) reported that FGF21 can enhance mouse cardiovascular health by inhibiting p53 signaling and stimulating mitochondrial biogenesis.

4.3. Crosstalk between FGF21 and somatotropic axis

FGF21 has close connections with the somatotropic axis, i.e. the growth hormone/insulin-like growth factor-1 (GH/IGF-1) signaling pathway (Fig. 2B). Hypothalamus controls the synthesis of GH in anterior pituitary gland via the release of GH-releasing hormone (GHRH). Consequently, GH

stimulates the expression of IGF-1 in liver. The GH/IGF-1 pathway has an important role in protein synthesis, glucose metabolism, cellular differentiation, and growth of the body (Bartke et al., 2013). Surprisingly, deficiencies in the function of somatotropic axis improve the healthspan and extend the lifespan, e.g. in mice (Bartke et al., 2013; Brown-Borg, 2015; Milman et al., 2016). For instance, Ames and Snell dwarf mice are deficient of GH whereas there is a mutation in the *GHRH* receptor gene in the Little mouse. A reduced GH secretion induces a decline in the level of serum IGF-1 and subsequently decreases IGF-1 signaling. There is convincing evidence that an elevated IGF-1/insulin signaling reduces the lifespan of several model organisms (Guarente and Kenyon, 2000). There is a mutual crosstalk between FGF21 and the somatotropic axis (Fig. 2B) which might explain the FGF21-induced extension of lifespan. For instance, transgenic mice overexpressing FGF21 showed evidence of GH resistance in liver which significantly reduced the level of serum IGF-1 (Inagaki et al., 2008; Zhang et al., 2012). Inagaki et al. (2008) demonstrated that FGF21 blunted the GH signaling in liver by inhibiting STAT5 signaling and increased the expression of IGF-1 binding protein 1 (IGFBP1) and suppressor of cytokine signaling 2 (SOCS2). Subsequently, the overexpression of FGF21 reduced the growth of mice but extended their lifespan (Inagaki et al., 2008; Zhang et al., 2012). Interestingly, an elevated expression of ATF4 has been observed in many slow-aging mice, e.g. in dwarf-mice (Li et al., 2014). On the other hand, Chen et al. (2011) demonstrated that acute treatment of mice with GH induced the expression of FGF21 in liver and increased the level of serum FGF21 (Fig. 2B). They also reported that the induction of FGF21 in liver was caused by the GH-induced lipolysis in adipose tissue and it was the release of FFA that induced FGF21 expression in liver. Moreover, Yu et al. (2012) observed that GH exposure also increased the expression of FGF21 in liver by enhancing the transactivation of the *FGF21* gene through the GH-activated STAT5 factor. It seems that there is a negative feedback loop between GH and FGF21.

The GH/IGF-1 axis activates the PI3K/AKT signaling pathway in peripheral tissues. With respect to the regulation of longevity, the mammalian target of rapamycin complex 1 (mTORC1) and forkhead box O (FOXO) pathways are the two most important targets of AKT signaling (van der Horst and Burgering, 2007; Johnson et al., 2013). There is abundant evidence that the AKT-induced

activation of mTORC1 can enhance the aging process, e.g. by inhibiting autophagy (Fig. 2A). Moreover, many longevity factors, e.g. AMPK activation, dietary restriction, and rapamycin, inhibit the function of mTORC1 (Johnson et al., 2013). Interestingly, Gong et al. (2016) demonstrated that FGF21 exposure inhibited the activation of mTORC1 in liver and increased hepatic insulin sensitivity in mice. They also reported that the hepatic knockdown of β-klotho prevented the FGF21-induced inhibition of mTORC1 signaling. These studies indicated that FGF21 suppressed the AKT/mTORC1 signaling in liver and controlled many hepatic mTORC1-dependent functions, e.g. lipogenesis (Ricoult and Manning, 2013). On the other hand, FGF21 induced mTORC1 activation in mouse adipose tissue (Minard et al., 2016). Minard et al. (2016) observed that FGF21 activated mTORC1 via the MAPK signaling pathway rather than through the AKT pathway. They also reported that the FGF21-induced activation of mTORC1 stimulated glucose uptake and adiponectin secretion in adipocytes. These studies emphasize that there are tissue-specific differences in the crosstalk between FGF21 and IGF-1/AKT/mTORC1 signaling.

4.4. FGF21 controls adiponectin-enhanced healthspan

FGF21 is an endocrine hormone involved in interorgan communication, e.g. it can regulate the secretion of adipokines and hormones of HPA axis (Lin et al., 2013; Liang et al., 2014; Hui et al., 2016). Adiponectin is an important target of FGF21 signaling in adipose tissues and the FGF21-adiponectin axis controls energy metabolism, e.g. glucose homeostasis and insulin sensitivity, as well as maintains vascular homeostasis (Lin et al., 2013; Hui et al., 2016). For instance, adiponectin controls several metabolic processes in skeletal muscles (Yoon et al., 2006; Li et al., 2017), liver (Liu et al., 2012b; Combs and Marliss, 2014), and brain (Thundyil et al., 2012). Many of the energy-related metabolic effects of adiponectin are mediated through the AMPK signaling pathway (Thundyil et al., 2012; Combs and Marliss, 2014; Salminen et al., 2017) (Section 4.2.). Given that FGF21 can reduce ER stress (Section 2.2.), Guo et al. (2017) reported that FGF21 administration reversed the suppression of adiponectin expression in adipose tissue of obese mice by alleviating ER stress. FGF21 can also enhance adiponectin secretion from adipose tissue by reducing the accumulation of

sphingolipid ceramide in obese mice (Holland et al., 2013). It is known that adiponectin stimulates mitochondrial biogenesis in skeletal muscles, thus enhancing glucose and lipid oxidation (Yoon et al., 2006; Qiao et al., 2012; Li et al., 2017). Adiponectin can also promote autophagy and thus maintain cellular proteostasis (Li et al., 2015; Liu et al., 2015b). Adiponectin protects against many age-related diseases improving healthy aging, e.g. it can alleviate cardiovascular diseases (Hopkins et al., 2007), metabolic syndrome (Whitehead et al., 2006; Padmalayam and Suto, 2013), hepatic steatosis (Ha et al., 2011), and ischemic diseases (Shibata et al., 2005; Joki et al., 2015; Ding et al., 2016). Although the serum levels of adiponectin are reduced in several aging-associated diseases, it seems that there exist no systematic changes in adiponectin levels with aging.

4.5. FGF21 inhibits inflammatory responses and immunosenescence

FGF21 has an important role in the protection against inflammatory responses and immune senescence (Zhang et al., 2013; Wang et al., 2015b; Singhal et al., 2016; Youm et al., 2016). For instance, a lack of FGF21 can provoke many inflammatory diseases, e.g. steatohepatitis (Liu et al., 2016) and pancreatitis (Singhal et al., 2016). Several studies have revealed that FGF21 exposure inhibited inflammation by attenuating the NF-κB signaling, a major inducer of inflammatory responses (Lee et al., 2012; Yu et al., 2015b; Xu et al., 2016; Yu et al., 2016). Yu et al. (2016) demonstrated that FGF21 treatment repressed the expression of many cytokines induced by lipopolysaccharide (LPS) exposure in murine macrophages. FGF21 also suppressed the LPS-induced ROS production and increased the expression of antioxidant enzymes in these macrophages. These responses were generated by inhibiting NF-κB signaling and increasing the expression of nuclear transcription factor-E2-related factor 2 (NRF2). FGF21 administration also attenuated the dimethylnitrosamine-induced hepatic fibrogenesis in mouse liver through the inhibition of NF-κB and TGF-β/Smad pathways (Xu et al., 2016). Given that AMPK activation is a potent inhibitor of the NF-κB signaling (Salminen et al., 2011), it is likely that FGF21 inhibits NF-κB-mediated inflammatory responses through AMPK activation (Fig. 2A). An improved healthspan and even an extension of lifespan induced by FGF21 could be attributed to its capacity to inhibit the NF-κB system since a low-

grade inflammation has been associated with the aging process and many age-related diseases (Salminen et al., 2008; Salminen and Kaarniranta, 2010b). However, there are many observations that chronic inflammatory conditions significantly elevated the level of serum FGF21, e.g. human sepsis and systemic inflammatory response syndrome (Gariani et al., 2013), pancreatitis (Shenoy et al., 2016), and chronic hepatitis (Kukla et al., 2012). This response could be caused by a significant inhibition of β-klotho expression induced by inflammatory cytokines, e.g. TNF-α and IL-1β, thus impairing the FGF21-mediated signaling (Diaz-Delfin et al., 2012; Zhao et al., 2016). The suppression of β-klotho expression is probably a negative feedback mechanism to combat against chronic activation of FGF21 signaling which might generate FGF21 resistance, a phenomenon observed in many chronic inflammatory conditions (Section 5.).

The involution of the thymus is a common hallmark of the aging process in vertebrates preceding many age-related changes in other tissues. The degeneration of thymus is responsible for a functional decline in adaptive immunity, e.g. loss of naïve T cells and decrease in T cell diversity, simultaneously with atrophy and accumulation of fat into thymus (Dixit, 2012; Palmer, 2013). Yang et al. (2009a) revealed that caloric restriction reduced thymic adipogenesis and consequently attenuated functional decay of thymus with aging. Moreover, obesity accelerated the thymic aging process and thus compromised the host's immune defence systems (Yang et al., 2009b). The age-related thymic involution has been attributed to metabolic dysfunctions in thymus and the deterioration is regulated by a close immune-metabolic interaction (Dixit, 2012). Recently, Youm et al. (2016) demonstrated that the overexpression of FGF21 in the tg-FGF21 mice (Section 3.) prevented the age-related adipogenesis and inflammatory changes as well as inhibited the decline in T cell functions during aging. In addition, they reported that the ablation of FGF21 (*FGF21*$^{-/-}$) in mice significantly accelerated the aging process of the thymus, e.g. the loss of naïve T cells. FGF21 treatment not only improves age-related immune maintenance in thymus but also in spleen. Li et al. (2016) reported that FGF21 exposure down-regulated the Th17-IL-17 axis in mouse spleen and subsequently alleviated type II collagen-induced arthritis. It is known that Th17-IL-17/23 signaling enhances tissue inflammatory reactions in autoimmune diseases (Korn et al., 2009). Li et al. (2016) observed that

FGF21 administration could reduce the expansion of Th17 cells and expression of inflammatory cytokines in the spleen of arthritic mice. Furthermore, FGF21 inhibited the STAT3-mediated differentiation of pro-inflammatory Th17 cells in spleen. Schmitt et al. (2013) revealed that the level of Th17 cells increased, whereas that of anti-inflammatory regulatory T cells (Tregs) declined with human aging which might increase the appearance of inflammatory diseases in the elderly.

5. FGF21 resistance: a risk for healthy aging?

Although FGF21 has a fundamental role in the enhancement of metabolism in several tissues, there is abundant evidence that the level of serum FGF21 has significantly increased in many metabolic and age-related diseases, e.g. obesity (Zhang et al., 2008; Gallego-Escuredo et al., 2015), fatty liver disease (Yilmaz et al., 2010; Yan et al., 2011), cardiovascular diseases (Chow et al., 2013; Domouzoglou et al., 2015), and type 2 diabetes (Roesch et al., 2015; Woo et al., 2017). In 2010, Fisher et al. demonstrated that obesity substantially reduced the responsiveness of liver and adipose tissue to FGF21, i.e. obesity is a FGF21-resistant state. Insulin resistance is also associated with obesity (Kahn and Flier, 2000). Patel et al. (2014) revealed that FGF21 administration conferred significant protection against global ischemia in the Langendorff-perfused hearts of lean rats, whereas the extent of cardioprotection was clearly reduced in the hearts of obese rats. They reported that obesity markedly reduced the FGF21-induced phosphorylation of ERK1/2, AKT, and AMPK which indicated that obesity lowered the sensitivity of cardiac muscle to FGF21 infusion. There are similar observations of FGF21 resistance in type 2 diabetes (Liu et al., 2015a). However, administration of high pharmacological levels of recombinant FGF21 or its analogs could revert FGF21 resistance by increasing the sensitivity of FGF21 signaling and thus these treatments were able correct the metabolic disorders (Coskun et al., 2008; Xu et al., 2009; Wu et al., 2011; Zhang and Li, 2014; Tanajak et al., 2016). Interestingly, Hanks et al. (2015) demonstrated that the circulation level of FGF21 increased linearly across the age groups (from 20-30 yrs to 65-80 yrs) in a healthy population. They also reported that the age-related increase in the serum FGF21 level was independent of body composition, e.g. fat percent and body mass index. There might be latent age-related diseases which could increase

the serum level of FGF21, e.g. a low-level of inflammation (Section 4.5.) and cellular stresses (Section 2.2.). Given that aging is the major risk factor for many aging-associated diseases, it seems that increased concentrations of serum FGF21 are not able to prevent the development of these metabolic diseases. One could postulate that aging is a FGF21 resistant state and thus elevates the individual's sensitivity to metabolic disorders. This hypothesis is supported by several observations from FGF21 knockout mice. Badman et al. (2009) observed that FGF21-deficient mice displayed impaired glucose and lipid homeostasis and they were prone to late-onset obesity. Moreover, the lack of FGF21 augments hepatic inflammation and steatohepatitis (Liu et al., 2016) as well as cardiac hypertrophy (Planavila et al., 2013) in mice. Although there are no studies on the effect of FGF21 deficiency on longevity, it seems that the knockout of FGF21 will jeopardize healthspan, similarly as FGF21 resistance.

The mechanisms underpinning FGF21 resistance have received only little attention although it might have a crucial role in healthy aging. There are many studies indicating that β-klotho protein, an obligatory co-receptor for FGF21 signaling, is required for the metabolic activity of FGF21, both *in vitro* and *in vivo* (Ogawa et al., 2007; Kharitonenkov et al., 2008; Ding et al., 2012). β-Klotho is expressed in tissues which are common targets of FGF21 signaling (Human Protein Atlas). Interestingly, the expression of β-klotho is down-regulated in many metabolic disorders which display an increase in FGF21 resistance, e.g. in adipose tissue of high-fat-diet induced obesity in non-human primates (Nygaard et al., 2014) or in the hearts of obese rats (Patel et al., 2014). Moreover, the expression of β-klotho was reduced in mouse non-alcoholic fatty liver disease, in association with the increased serum level of FGF21 (Rusli et al., 2016). So et al. (2013) demonstrated that the expression of β-klotho decreased in the pancreatic islets of diabetic *ob/ob* mice in an age-dependent manner and it also declined in normal pancreatic islets when these were exposed *ex vivo* to high glucose concentration. Concurrently, the expression of PPARγ was decreased and islets displayed a resistance to FGF21 exposure. Interestingly, the activation of PPARγ signaling with rosiglitazone prevented the down-regulation of β-klotho and attenuated FGF21 resistance in both the islets of *db/db* mice and isolated islets of normal mice. It seems that the down-regulation of PPARγ, observed in the FGF21-resistant state, could enhance the formation of FGF21 resistance in pancreatic islets. This conclusion is

consistent with the observations from mouse adipose tissue where FGF21 regulated the transcriptional activity of PPARγ and appeared to function in a feed-forward loop with PPARγ (Dutchak et al., 2012). It appears that this regulatory network can be controlled by the expression of β-klotho, since the overexpression of β-klotho sensitized FGF21 signaling in the adipose tissue of male mice and prevented diet-induced obesity (Samms et al., 2016).

Chronic inflammation is commonly involved in FGF21-resistant states, e.g. obesity and hepatic steatosis. Diaz-Delfin et al. (2012) demonstrated that the TNF-α-induced pro-inflammatory signaling repressed the expression of β-klotho in cultured adipocytes. They also revealed that the expression levels of both β-klotho and FGFR1 were clearly reduced in the adipose tissue of mice fed a high-fat diet. Rosiglitazone treatment normalized the expression levels of β-klotho and FGFR1 proteins in adipose tissue and in addition, it restored the serum concentration of FGF21 to the control level indicating that FGF21 resistance could be eliminated by the activation of the PPARγ signaling. Recently, Zhao et al. (2016) observed that IL-1β inhibited the expression of β-klotho in mouse liver. They revealed that the expression of β-klotho was repressed through the NF-κB and JNK1 pathways. These studies clearly demonstrated that inflammatory cytokines can suppress FGF21 signaling through the down-regulation of β-klotho and subsequently generate FGF21 resistance (Fig. 3). It is known that fasting/dietary restriction inhibits inflammatory responses thus alleviating metabolic disorders commonly associated with inflammation (Morgan et al., 2007; Crisostomo et al., 2010; Wanders et al., 2014). There are studies indicating that caloric restriction and methionine-deficient diet significantly increased the expression of β-klotho (Fletcher et al., 2012; Grant et al., 2016) which might enhance FGF21 signaling in tissues, especially since fasting increases FGF21 expression (Section 3). Moreover, Samms et al. (2016) showed that the overexpression of β-klotho in mouse adipose tissue increased its sensitivity to endogenous FGF21. These studies imply that fasting/dietary restriction may counteract the FGF21 resistance in tissues and thus enhance energy metabolism and improve healthspan.

MicroRNA-34a (miR-34a) is another potent inhibitor of the expression of β-klotho, thus being able to enhance FGF21 resistance (Fig. 3). Fu et al. (2012) demonstrated that miR-34a could directly

target the 3'UTR of β-klotho mRNA and inhibited the expression of β-klotho protein. More recently, Fu et al. (2014) observed that miR-34a was also able to bind to the 3'UTR of FGFR1 mRNA which attenuated FGF21 signaling. They reported that the down-regulation of miR-34a in dietary obesity increased FGF21 signaling and subsequently reduced the adiposity of obese mice. It is known that miR-34a has several metabolic gene targets, e.g. pro-longevity SIRT1 (Yamakuchi et al., 2008; Tabuchi et al., 2012), which could affect the metabolic regulation by miR-34a. The expression levels of miR-34a are increased in both obesity (Fu et al., 2014) and coronary artery disease (Tabuchi et al., 2012). Interestingly, several studies have revealed that the expression of miR-34a is robustly increased with aging in rat liver (Li et al., 2011a), mouse heart and spleen (Ito et al., 2010; Boon et al., 2013), mouse brain (Li et al., 2011b), and human heart (Boon et al., 2013). There are also studies indicating that miR-34 is able to modulate the ageing process in *Caenorhabditis elegans* (Yang et al., 2013) and *Drosophila* (Liu et al., 2012a) as well as accelerate cellular senescence in mammalian cells (Tazawa et al., 2007; Badi et al., 2015). Currently, it needs to be clarified whether the age-related increase in miR-34a expression can enhance FGF21 resistance and subsequently evoke the metabolic disorders commonly associated with the aging process.

6. Conclusions and perspectives

FGF21 possesses many crucial properties which impact on the aging process, i.e. it controls energy metabolism through complex interorgan crosstalk and moreover, it can act as a stress hormone. FGF21 is normally secreted from liver although during times of stress, it can be expressed and secreted from adipose tissues as well as skeletal and cardiac muscles and probably also from other tissues in response to local stresses. Since the integrated stress response pathway is a potent inducer of FGF21 expression, one can reasonably argue that FGF21 is also a common stress factor which modifies not only energy metabolism but can also activate many rescue processes either directly through activation of AMPK signaling and some other pathways or indirectly by stimulating the secretion of adiponectin and hormones of the HPA axis. It is no surprise that a stress-induced increase in the level of serum FGF21 can attenuate some acute metabolic disorders which could jeopardize the

healthy aging process. Moreover, metabolic deficiencies, e.g. dietary restriction and mitochondrial deprivations, increase the expression of FGF21 and can extend lifespan. There is convincing evidence indicating that energy metabolism and stress responses are intimately intertwined in the regulation of longevity. However, many of the chronic disorders associated with either metabolism or stresses can provoke FGF21 resistance, a phenomenon observed in many metabolic diseases and perhaps even in the normal aging process. Currently, it is known that inflammatory responses disturb the FGF21 signaling and subsequently can generate FGF21 resistance if inflammation becomes chronic. In the future, it will be important to clarify the mechanisms which induce resistance to FGF21 signaling since this may be a novel way to extend the healthy aging process.

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FIGURE LEGENDS

Fig. 1. Several nutritional and cellular stresses are associated with an increased level of serum FGF21. Most of these conditions also display an enhanced expression of FGF21 at the tissue level.

Fig. 2. Major signaling networks regulating longevity through FGF21 signaling. A. Integrated stress response pathway through the eIF2α-ATF4 axis activates the expression of FGF21. The AMPK signaling is a major downstream pathway stimulating autophagy and inhibiting NF-κB and mTORC1 signaling. B. Crosstalk between growth hormone and FGF21 signaling. Some of the connections are tissue-specific (see text). *Abbreviations:* AA, Amino acid; AMPK, AMP-activated protein kinase; ATF4, Activating transcription factor 4; eIF2α, Eukaryotic initiation factor 2α; ER, Endoplasmic reticulum; FGF21, Fibroblast growth factor 21; IGF-1, Insulin-like growth factor-1; mTORC1, Mammalian target of rapamycin complex 1; NF-κB, Nuclear factor-κB; SIRT1, Sirtuin 1.

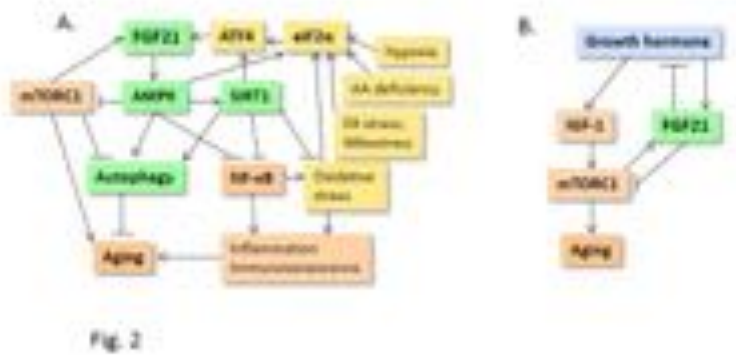

Fig. 2

Fig. 3. Generation of FGF21 resistance in tissues. The figure depicts those factors known to inhibit signaling through the FGFR1/β-klotho complex. Inflammatory factors IL-1β and TNFα, high glucose concentration, and miR-34a repress the expression of β-klotho and thus down-regulate FGF21 signaling. *Abbreviations*: FGFR1, Fibroblast growth factor receptor 1, IL-1β, Interleukin-1β; TNFα, miR-34a, MicroRNA-34a; TNFα, Tumor necrosis factor α.

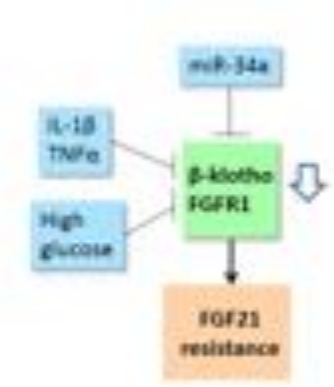

Fig.3