Fibroblast Growth Factor 21 - Metabolic Role in Mice and Men

Harald Staiger, Michaela Keuper, Lucia Berti, Martin Hrabě de Angelis, Hans-Ulrich Häring

Endocrine Reviews
Endocrine Society

Submitted: January 10, 2017
Accepted: July 25, 2017
First Online: July 28, 2017

FGF21 in mice and men

Fibroblast Growth Factor 21 - Metabolic Role in Mice and Men

Harald Staiger[1,2,3,4,5], Michaela Keuper[4,5], Lucia Berti[3,4,5], Martin Hrabě de Angelis[4,5,6], Hans-Ulrich Häring[2,3,5,7]

[1] *Institute of Pharmaceutical Sciences, Department of Pharmacy and Biochemistry, Eberhard Karls University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany*

[2] *Interfaculty Centre for Pharmacogenomics and Pharma Research at the Eberhard Karls University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany*

[3] *Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the Eberhard Karls University Tübingen, Otfried-Müller-Straße 10, 72076 Tübingen, Germany*

[4] *Institute of Experimental Genetics, Helmholtz Center Munich, German Research Center for Environmental Health, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany*

[5] *German Center for Diabetes Research (DZD), Ingolstädter Landstraße 1, 85764 Neuherberg, Germany*

[6] *Chair for Experimental Genetics, Technical University Munich, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany*

[7] *Department of Internal Medicine, Division of Endocrinology, Diabetology, Angiology, Nephrology, and Clinical Chemistry, University Hospital Tübingen, Otfried-Müller-Straße 10, 72076 Tübingen, Germany*

Received 10 January 2017. Accepted 25 July 2017.

Since its identification in 2000, the interest of scientists in the hepatokine fibroblast growth factor (FGF) 21 has tremendously grown, and still remains high, due to a wealth of very robust data documenting this factor's favorable effects on glucose and lipid metabolism in mice. For more than ten years now, intense *in vivo* and *ex vivo* experimentation addressed the physiological functions of FGF21 in humans as well as its pathophysiological role and pharmacological effects in human metabolic disease. This work produced a comprehensive collection of data revealing overlaps in FGF21 expression and function but also significant differences between mice and men that have to be considered before translation from bench to bedside can be successful. This review summarizes what is known about FGF21 in mice and humans with a special focus on this factor's role in glucose and lipid metabolism and in metabolic diseases, such as obesity and type-2 diabetes mellitus. We highlight the discrepancies between mice and men and try to decipher their underlying reasons.

This article summarizes what is known about FGF21 in mice and humans with a special focus on this factor's role in glucose and lipid metabolism and in metabolic diseases.

Essential Points

- Fibroblast growth factor (FGF) 21 is a liver-derived circulating hormone (hepatokine) with very robust favorable effects on glucose and lipid metabolism in mice.
- First clinical trials with FGF21 analogues in type-2 diabetic patients revealed improvements in plasma lipids, but also an unexpected lack of glucose-lowering efficacy.
- Differences between mice and humans in FGF21's tissue expression and physiological functions may underlie unexpected clinical findings.
- A better understanding of FGF21's role in human physiology and pathophysiology will facilitate the translation of experimental findings from bench to bedside.

- In both mice and men, FGF21 exerts adverse effects on bone mass and density, and this has to be taken into account in the development of FGF21-based therapeutics.

Abbreviations

AMPK – AMP-activated protein kinase; apo – apolipoprotein; ATF – activating transcription factor; ATGL – adipose triglyceride lipase; BAT – brown adipose tissue; BMAL – brain and muscle aryl hydrocarbon receptor nuclear translocator-like; BMI – body mass index; CLOCK – circadian locomoter output cycles protein kaput; CoA – coenzyme A; CPT – carnitine palmitoyltransferase; CREB – cAMP-response element-binding protein; CRH – corticotropin-releasing hormone; DPP – dipeptidyl peptidase; E4BP – E4-binding protein; Egr – early growth response; eIF – eukaryotic translation initiation factor; ER – endoplasmic reticulum; ERK – extracellular signal-regulated kinase; FAS – fatty acid synthase; FFA – free fatty acids; FGF – fibroblast growth factor; FGFR – FGF receptor; Fox – forkhead box; GH – growth hormone; GLUT – glucose transporter; HDL – high-density lipoprotein; HFD – high-fat diet; HPA – hypothalamic-pituitary-adrenal; HSL – hormone-sensitive lipase; IGF – insulin-like growth factor; IGFBP – IGF-binding protein; LDL – low-density lipoprotein; MAPK – mitogen-activated protein kinase; MHO – metabolically healthy obese; mTOR – mammalian target of rapamycin; MUHO – metabolically unhealthy obese; PEG – polyethylene glycol; PGC – PPARγ coactivator; PI – phosphoinositide; PPAR - peroxisome proliferator-activated receptor; ROR – retinoic acid receptor-related receptor; Sirt – sirtuin; SNP – single nucleotide polymorphism; SREBP – sterol regulatory element binding protein; STAT – signal transducer and activator of transcription; STK – serine/threonine kinase; T2D – type-2 diabetes mellitus; UCP – uncoupling protein; WAT – white adipose tissue

I. Introduction

With a prevalence of about eight percent in adults, type-2 diabetes mellitus (T2D) is the most prominent metabolic disease worldwide (WHO Fact sheet Diabetes at http://www.who.int/mediacentre/factsheets/fs312/en). The hallmark of the disease, i.e., hyperglycemia, results from insulin resistance of liver, skeletal muscle, adipose tissue, and brain and a concomitant failure of pancreatic β-cells to compensate for this resistance by increased insulin secretion (1). Current therapeutic options aim at reducing insulin resistance (metformin, thiazolidinediones), enhancing insulin secretion (sulfonylureas, meglitinides, dipeptidyl peptidase [DPP] IV inhibitors, incretin mimetics), or excreting glucose via the urine (sodium/glucose cotransporter 2 inhibitors), but a progressive loss of β-cell function and mass is often observed (2). Eventually, the ultima ratio to normalize blood glucose is the replacement of endogenous insulin by injection of human recombinant insulin or insulin analogues. New insights into the molecular pathomechanisms behind insulin resistance and β-cell failure point towards a crucial role for a well-balanced humoral crosstalk between metabolic relevant tissues (e.g. adipose, muscle, liver). Highly relevant players and promising targets for novel therapeutic strategies in this crosstalk were recently identified, among them fibroblast growth factor 21 (FGF21) (3–5). FGF21 is an endocrine factor secreted by liver acting as a metabolic regulator. The interest in FGF21's metabolic effects was aroused by the emergence of FGF21 as hit in a screen testing secreted proteins of unknown function for stimulation of glucose uptake in murine 3T3-L1 adipocytes in an insulin-independent manner (6). Based mainly on preclinical studies in mice showing improvements in glucose- and lipid metabolism, FGF21 emerged as an interesting new candidate for T2D treatment, and several pharmaceutical companies made huge efforts to put this idea into practice. However, the glucose-lowering potential of FGF21 in humans has been questioned.

II. Molecular biology of FGF21 in mice and men

A. FGF21 gene and gene products

In 2000, murine and human FGF21 were identified and characterized at the cDNA level by Nishimura *et al.* (7). The murine gene is located on chromosome 7, consists of three coding exons, and gives rise to a single transcript that encodes a pre-protein of 210 amino acids (aa)

including an N-terminal signal peptide of 28 aa. The secreted form has an apparent molecular weight of ~23 kDa (182 aa). The human orthologous gene resides on chromosome 19, likewise consists of three coding exons (and one non-coding 5'-flanking exon), and gives rise to two transcripts due to usage of alternative promoters. Both transcripts encode the same pre-protein of 209 aa including a signal peptide of 28 aa. Human FGF21 shares 146 aa with the murine orthologue (79% identity) and the secreted form has an apparent molecular weight of ~23 kDa (181 aa).

B. FGF21 and the FGF superfamily

Depending on the species, between 19 and 27 FGF genes were identified in vertebrates (8). In mice and humans 22 genes (FGF 1-23) exist which can be phylogenetically grouped into eight subfamilies (8). Functionally, FGFs may be grouped into three subfamilies: Intracellular FGFs (FGF 11-14) that lack a signal peptide, FGFs (FGF19 (murine orthologue: FGF15) and FGF21) with low heparin-/heparan sulfate-binding capacities indicating release into circulation and systemic action, and the remaining FGFs with high heparin-/heparan sulfate-binding capacities thus potentially mainly acting in an auto/paracrine manner (9).

C. FGF21 receptors and their signaling

At target sites, FGF21 binds and activates members of the FGF receptor (FGFR) family of receptor tyrosine kinases. Mammals have seven primary FGFR isoforms (1b, 1c, 2b, 2c, 3b, 3c, and 4) (10). FGFR activation by FGF21 *in vitro* and *in vivo* is crucially dependent on β-Klotho (KLB), an FGFR-binding single-pass transmembrane protein (11–15). Accordingly, a clear preference of FGF21 for FGFR1c-KLB and FGFR3c-KLB complexes have been demonstrated (13,16). Activation of these complexes by FGF21 leads to a plethora of rapid signaling events (review of general FGF signaling (17)). Among these, the hitherto best described events are phosphorylation of FGFR substrate 2α and subsequent activation of the mitogen-activated protein kinase (MAPK) cascade including Raf-1 and extracellular signal-regulated kinases (ERK) 1 and 2 (6,11,18–21). Interaction of FGF21 with FGFR4-KLB is very weak and does not induce ERK phosphorylation (10,22).

D. Tissue specificity of FGF21 and FGF21 receptor gene expression

In the initial paper discovering FGF21, Nishimura *et al.* reported predominant expression of the murine FGF21 gene in liver and lower mRNA levels also in thymus (7). This preliminary picture has been modified and several studies reported, although too a much lower extent, expression of FGF21 mRNA also in pancreas, testes, gastrointestinal tract, brain, skeletal muscle, brown and white adipose tissue (BAT and WAT, respectively) (23,24). In humans, the FGF21 gene under basal conditions is considered to be nearly exclusively expressed in liver, and weaker signals were shown in the brain (24) and, according to unpublished results, in the pancreas (25) (Figure 1).

Since FGFR1 and FGFR3 are rather ubiquitously expressed in mice and humans, FGF21's target organ selectivity is probably determined by the restricted tissue expression of β-Klotho: in keeping with a previous report by Ito *et al.* (26), large-scale RNA sequencing data reveal that the murine β-Klotho gene is predominantly expressed in liver, pancreas, and adipose tissue (no KLB expression in muscle) (24). In humans, major β-Klotho expression sites are, beyond liver and adipose tissue, breast and bone marrow. Only weak expression signals are observed in human pancreas (24). It is conceivable that differences at the β-Klotho expression level between mice and men may contribute to some of the divergent findings regarding FGF21's metabolic actions described for the two species.

E. FGF21 in the circulation

Serum FGF21 concentrations measured in chow-fed mice range from 0.1 to 1 ng/mL (19,27–29) depending on the strain tested, the age of the mice, and the assay used. Serum concentrations of healthy humans exhibit marked inter-individual variation ranging from 5 pg/mL to 5 ng/mL (30–34).

As to FGF21's stability in blood, only limited information is available for the half-life of human recombinant (non-glycosylated) FGF21 with slightly deviating data ranging from 20 min to 2h in different mice strains, rats and cynomolgus macaques (18,35–37). Thus, a half-life of less than 2h can be assumed for human recombinant FGF21. The *in vivo* stability of endogenous glycosylated FGF21 in animals and humans is currently unknown. However, as glycosylation generally confers relative resistance to proteolysis, we anticipate that the physiologically occurring FGF21 form has an appreciably longer half-life in the circulation compared to the bacterially produced recombinant protein.

Very recently, Zhen *et al.* characterized major cleavage events during proteolytic inactivation of human FGF21 in the circulation (38): these include two N-terminal cleavage events after proline residues 2 and 4 catalyzed by DPPIV and/or fibroblast activation protein (FAB) and one C-terminal cleavage event after proline 171 probably catalyzed by FAB (39). As the C-terminus is important for β-Klotho binding and overall activity of FGF21 (40,41) inhibitors targeting FAB may increase full-length, active FGF21 blood concentrations. This however remains to be tested.

III. Regulation of FGF21 in mice and men

In humans, FGF21 is considered nearly exclusively produced by liver and data from liver-specific knockout animals suggest that circulating FGF21 in mice mainly derives from liver (42). FGF21 is, however, also expressed in several key metabolic tissues (see section II, paragraph D), and certain physiological stimuli and pathological conditions provoke considerable increments in these extrahepatic expression sites which may influence this hormone's circulating levels. Additionally, there may be metabolically relevant roles of locally produced FGF21, e.g., in pancreas, brain, muscle or adipose tissue (43,44).

A. Nutritional regulation

Nutrient deprivation/fasting, lipid intake via suckling, and consumption of ketogenic diets (i.e. high-fat low-carbohydrate diet designed to simulate the fasting state) result in several-fold raise of FGF21 serum levels in mice which seems to be a result of increased blood concentrations of free fatty acids (FFA) which activated PPARα-dependent FGF21 gene induction in liver (29,45–47). Contrasting the FGF21 induction by FFA in mice, elevation of plasma FFA in humans does not increase, but rather decrease circulating FGF21 concentrations as shown in two larger studies of healthy volunteers during a lipid tolerance test (48,49). Furthermore, humans demonstrate a huge inter-individual range of FGF21 levels and the effect of fasting (up to 48h) on FGF21 blood concentrations are not consistent, either showing no effect, only modest increased levels or even a drop in FGF21 levels (30,31,33,50). One explanation for this discrepancy between mice and men might be the overall higher metabolism of mice as compared with men. Accordingly, elevations of FGF21 are only seen in humans after prolonged fasting periods of at least seven days (30,31). In line, mice fasted for 8h demonstrate no difference in FGF21 expression (29). Therefore, the physiological role for human FGF21 in adaption to starving is still under debate.

Although the contribution to circulating FGF21 levels is questionable, starvation regulates FGF21 expression in extrahepatic tissues: gene and protein expression of FGF21 in the pancreas are reduced upon fasting in mice (51). Pancreatic FGF21 expression, however, does supposedly not contribute to circulating levels. A recent murine study rather suggests that pancreatic FGF21 acts in an autocrine/paracrine manner as a pancreatic secretagogue to

prevent ER stress/protein overload (43). Human data are still missing. Muise *et al.* demonstrated that fasting and high-fat diet (HFD), probably via FFA-mediated PPARγ activation, induce the FGF21 gene in murine adipose tissue (52). Although not a predominant expression site, FGF21 is upregulated in skeletal muscle upon fasting (53). Jiang *et al.* investigated FGF21's role in testes and found that, in contrast to liver, testicular FGF21 expression is not regulated by fasting (54). Regarding thymic FGF21 (major expression site in mice), a recent mouse study demonstrates that the age-related decline in thymic FGF21 expression could be restored by caloric restriction (55).

Sugar ingestion (high-carb diets), in particular fructose, acutely provokes changes in FGF21 blood levels and hepatic expression in mice and men (56–60). Within two hours after fructose ingestion, FGF21 concentrations raise 3.4-fold in humans (60) and after 1 hour in mice a 2-fold increase of FGF21 has been reported, which seems to be dependent on ChREBP (58,59). Glucose led only to a modest and delayed increase in FGF21 levels in humans (60). The robust effect of fructose on FGF21 levels in mice and men is intriguing. Together with mouse data showing FGF21-induced suppression of sugar ingestion (59) and that sweet preference induced by FGF21 is dependent on KLB expression in the brain (61), provide evidence for a novel negative feedback loop along the liver-brain axis regulating sugar consumption. A similar mechanism by which FGF21 acts on the reward system in the brain to regulate food intake has now been indicated in humans (62).

Ketogenic diet (KD) strongly induces FGF21 in liver and increases its circulating levels in mice (29). In humans (healthy and obese/diabetic), KD does not increase FGF21 serum levels (30,33,50) and even decreases its levels in obese patients when KD was combined with low calorie intake (63). The observation that, upon long-term fasting, ketone bodies appear in the circulation days before FGF21 levels begin to rise (30) additionally argues against a regulating role for FGF21 in ketogenesis in humans. One has to consider, however, that KD used for mouse studies have lower protein content than control (chow) diet (9.5 vs 23.5 % wt/wt) (29,64–66) whereas human KD are usually well controlled for adequate protein content and sometimes are even combined with high protein intake (63). Accordingly, supplementation of the murine KD with methionine almost completely prevented the KD-induced FGF21 induction (67). Several studies demonstrated that hepatic FGF21 production is robustly induced by amino acid deprivation and protein restriction, both mediated by the eIF2α-ATF4-CHOP axis of the endoplasmic reticulum (ER) stress response in mice (66,68–71). Just as in mice, FGF21 blood levels increase in humans in response to dietary protein restriction (1.7-fold after 4 weeks (66) and ~2 fold after 6 weeks (72)). Although the human FGF21 gene was identified as a target for ATF4 in cell culture experiments (71), the involvement of the ER stress involving eIF2α-*ATF4* pathway in vivo was not addressed in humans yet. Recently, with a nutritional modeling platform using data of mice that were fed with one of 25 diets varying in protein, carbohydrate, fat, and total energy density, a major role for low protein intake driving FGF21 expression/secretion has been demonstrated with a maximal FGF21 induction when low protein content was coupled to high carbohydrates (57). It appears that FGF21 levels and its metabolic actions are strongly coupled to the macronutrient composition of the mouse diet, an observation that should be considered in human studies where diet cannot be controlled as tight as in murine studies.

B. Exercise

Interestingly, Kim *et al.* reported that acute exercise elevates FGF21 blood levels in mice and men, and this was associated with a rise in circulating FFA and enhanced hepatic expression of FGF21, PPARα, and ATF4, but not with altered FGF21 gene expression in skeletal muscle or adipose tissue (73). Thus, exercise promotes hepatic FGF21 production probably via adipose tissue lipolysis and subsequent fatty acid signaling and ER stress in liver. In humans, different exercise regimens stimulate FGF21 production in liver and increase blood FGF21

(74–77). Hansen *et al.* demonstrated that circulating glucagon which rises during exercise enhances hepatic FGF21 production in humans (76,77) indicating a muscle-pancreas-liver axis being responsible for elevated FGF21 blood levels upon exercise.

C. Hormonal regulation

As mentioned above, hepatic FGF21 expression and circulating FGF21 levels are increased by glucagon (via AMPK and PPARα) in mice and humans (78,79). Additionally, insulin moderately increases the FGF21 blood concentration in mice under hyperinsulinemic-euglycemic clamp technique (80–83). In line, human skeletal muscle does express appreciable amounts of FGF21 under hyperinsulinemia (82–84). This increased expression, however, does not significantly contribute to circulating FGF21 levels (82,84). Interestingly, human data indicate suppression of FGF21 secretion from liver by insulin which contrasts mouse data showing no difference in FGF21 levels in liver-specific insulin receptor knockout (LIRKO) mice (85). Growth hormone (GH) acutely increases FGF21 serum levels (2.5 fold after 2h, 10-fold peak at 6h) in mice, but this seems to be dependent on adipose lipolysis (86). In healthy humans, GH had no acute effect on serum FGF21 levels (after 3h) (87). In mice, additional hormonal stimuli of hepatic FGF21 expression include thyroid hormones (TH) (via TH receptor β, retinoid X receptor, and PPARα) (88,89) and glucocorticoids (via glucocorticoid receptor) (90). The effect of these hormones on FGF21 levels in humans has not been addressed in detail so far. No difference in FGF21 in hyperthyroidism or after treatment with the liver-selective TH analogue eprotirome argues against regulation of FGF21 levels by thyroid hormones in humans (91).

D. Circadian rhythm

A circadian rhythmicity of circulating FGF21 with high levels during the fasting state and low levels during feeding has been reported for both, mice and men (92,93). Andersen *et al.* reported circadian rhythmicity of human FGF21 blood levels during a 72-hour fast with peak levels at 02:30 a.m. and nadirs at 08:30 a.m. (94). As there are three circadian-responsive elements (E-box, D-box, and a ROR-response element site) which are hallmarks of a classical circadian-regulated gene are located in the FGF21 promotor (93,95,96), a direct control of FGF21 levels by the core clock machinery is possible. In primary murine hepatocytes, insulin induced circadian output protein (i.e. E4BP4), which is a repressor of the FGF21 promoter (92). Nevertheless, circadian FGF21 expression in murine liver seems to be dependent on PPARα in mice (93), and in humans oscillating FFA levels match those of FGF21 (97). Thus, insulin and FFA are physiological signals that may explain the circadian rhythmicity of circulating FGF21 with high levels during the fasting state (during the night) and low levels during feeding (92,93,97).

E. Cold exposure

In BAT and WAT, but not in liver, cold exposure and adrenergic signaling potently induce FGF21 gene expression in mice and men (98–102). The pathway of cold-induced FGF21 induction includes cyclic AMP, protein kinase A, p38 MAPK, and ATF2 (100). Notably, some reports show an increase in serum FGF21 levels indicating that under certain conditions adipose tissue may contribute to circulating levels in mice and humans (100,101). No direct mouse and human data are available, but in rats a difference in arteriovenous concentrations of plasma FGF21 across interscapular BAT has been demonstrated further arguing for BAT as a source of circulating FGF21 (100). In line, BAT of cold exposed UCP1 knockout mice is the source of circulating FGF21 (103), thus at least in rodents, adipose tissue might contribute to circulating levels under distinct conditions.

F. PPAR agonists

Treatment with PPARγ agonists (thiazolidinediones), clinically used as insulin sensitizers, does not alter human FGF21 blood levels in humans (50,80,104). In line, PPARγ agonist-

treated mice have increased FGF21 protein levels in WAT but no elevated circulating levels (27). Treatment with PPARα-activating fibrates increases human FGF21 blood levels pointing to a role of this FFA-dependent transcription factor in FGF21 gene induction reminiscent of that in mice, at least in this pharmacological setting (30,50,104,105). While selective PPARγ agonists induce FGF21 in adipose tissue but not in liver, selective PPARα agonists do this in liver but not in adipose tissue (27,52), reflecting these PPARs' tissue specificity. Although, one mouse study demonstrates that PPARγ agonist treatment results in FGF21 secretion of WAT concomitantly with elevations in plasma FGF21 (52), future studies are needed to explore if and under which condition WAT is contributing to circulating levels in particular in humans. It is certain to say that WAT-FGF21 acts locally as an autocrine/paracrine factor in mice and men.

In summary (Figure 2), the main expression and secretion site in mice and men is the liver. Beside the above mentioned stimuli, hepatic FGF21 expression is regulated by bile acids (via farnesoid X receptor) (106) and dietary supplements/drugs such as all-trans-retinoic acid (via retinoic acid receptor β) (107), α-lipoic acid (via cyclic AMP response element-binding protein H) (108), and resveratrol (via SIRT1) (109,110). This list demonstrates that hepatic FGF21 expression in mice and men is under complex nutritional and hormonal control and is regulated by multiple transcription factors in a combinatorial way with a network of nuclear receptors being of central importance. As to the regulation of circulating FGF21, mice and humans share the following physiological stimuli: nutrition (protein restriction, fructose ingestion), exercise (via pancreatic insulin and glucagon) and, to a lesser extent, circadian clock machinery.

IV. FGF21 in metabolic disease

Several metabolic disorders are associated with increased FGF21 levels in mice and humans. In the following section we will discuss metabolic diseases which demonstrate altered FGF21 levels with a special focus on human data. The reason for increased serum FGF21 in these pathological conditions is largely unknown (potential FGF21 resistance will be discussed at the end of the section).

A. Obesity

Genetic and diet-induced murine models of obesity, such as *ob*/*ob* and HFD-fed C57BL/6 mice, display several-fold increased serum FGF21 concentrations (up to 3 ng/mL) that are accompanied by increased FGF21 gene expression in liver and to a lesser extent in WAT (19,111). In humans, FGF21 blood concentrations positively associate with body mass index (BMI) and whole-body, visceral, pericardial, and epicardial fat mass and are elevated in the obese state (32,33,81,104,112–116). Overfeeding-induced gain of weight and body fat results in elevated human FGF21 concentrations (117,118). By contrast, acute and pronounced weight and body fat loss due to bariatric (Roux-en-Y gastric bypass) surgery does not lead to reductions in circulating FGF21 (119,120) evidencing that adipose tissue is not a source of circulating FGF21 in humans.

B. Metabolically unhealthy obesity

Common obesity can be dissociated into two subtypes: metabolically healthy obesity (MHO) without serious metabolic complications (~20-40%), whereas the remainder is metabolically unhealthy obesity (MUHO) characterized by insulin resistance, increased visceral fat mass, ectopic fat deposition in skeletal muscle and liver, inflamed adipose tissue and liver, and increased intima-media thickness of the carotid artery (121–124). Recently, Berti *et al.* demonstrated that FGF21 blood levels are more than two-fold higher in MUHO as compared to body fat-matched MHO subjects, and the authors suggested that this reflects an adiposity-independent role of FGF21 in the metabolic derangements of MUHO (125). This is in

agreement with studies, e.g., reporting BMI- and body fat mass-independent positive associations of FGF21 levels with insulin resistance (126,127).

Mouse models of obesity-associated diseases, like non-alcoholic fatty liver disease, chronic hyperglycemia, and atherosclerosis, consistently reveal increased FGF21 blood levels (128–131). Also in humans, FGF21 levels are increased in several obesity-associated disorders and the metabolic syndrome (32,113,132,133).

C. Fatty liver and diabetes

The strongest BMI-independent determinant of hepatic FGF21 production and circulating FGF21 concentrations is liver fat content (134–137), and fatty liver is a hallmark of MUHO (121). Accordingly, FGF21 blood concentrations are consistently elevated in patients with non-alcoholic fatty liver disease and steatohepatitis (33,134–136,138–140). With respect to the prominent role of fatty liver in the pathogenesis of T2D (for review, see (141)), it is not unexpected that FGF21 blood levels are increased in prediabetic dysglycemia (34,142–144), T2D (81,142–147), gestational diabetes (148,149), and diabetic retinopathy (150,151). Additionally, in the blood of patients with (diabetic) nephropathy elevated FGF21 concentrations were measured which may derive from reduced glomerular filtration rates (152–157).

D. Lipid profile and vascular complications

Higher circulating FGF21 concentrations associate with atherogenic lipid profiles, i.e., increased plasma triglycerides, total and low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol (32,34,104,113,114,137,158–162). Among these lipids, circulating FGF21 most robustly correlates with plasma triglycerides possibly reflecting its strong association with hepatosteatosis and steatosis-related increased very-low-density lipoprotein secretion.

Elevated FGF21 blood levels with metabolic syndrome together with increased intima-media thickness, arterial stiffness, and atherosclerotic plaque formation (147,163–167), as well as coronary artery/heart disease (158,161,168), and acute myocardial infarction (169) argue for a complex, i.e., liver-fat-dependent and -independent, relationship of this hormone with vascular complications. This is additionally strengthened by FGF21's association with hypertension (126,158,160,162,165,170) and preeclampsia (171).

E. Bone diseases

In keeping with FGF21's inhibitory action on bone formation in mice (172), Hanks *et al.* reported an inverse relationship between circulating FGF21 and bone mineral density measured by dual energy X-ray absorptiometry in humans (173). Moreover, elevated FGF21 levels are associated with reduced bone strength and worsened bone microarchitecture (decreased trabecular number and increased trabecular separation in the radius) (174) and with bone loss in knee osteoarthritis (175).

F. Muscle diseases

In mouse models, manipulations inducing metabolic dysregulation in muscle lead to the induction and release of FGF21 from muscle: Izumiya *et al.* reported that muscle-specific transgenic Akt1 overexpression increases FGF21 expression and blood concentrations, providing evidence that muscle-derived FGF21 can be of systemic relevance (53). Mitochondrial myopathy, a stress situation accompanied by Akt activation, is associated with FGF21 gene induction in skeletal muscle (176). Additionally, muscle-specific autophagy knockouts (ATG7) demonstrate mitochondrial-stress-ATF4-dependent increased FGF21 expression in muscle, but not in liver, WAT or BAT, and an increase in serum FGF21 levels (177). Similar regulation of the FGF21 gene is seen in heart muscle: fasting and ER stress, the latter resulting from intracellular triglyceride overload due to whole-body deficiency of adipose triglyceride lipase (ATGL), provoke marked increases in FGF21 expression (178).

Induction of muscular ER stress (evidenced by eIF2α and ATF4 activation) by ectopic expression of uncoupling protein 1 results in markedly enhanced FGF21 gene expression in muscle, but not in liver or adipose tissue, and in five-fold higher FGF21 blood levels even in the absence of myopathy (179). Likewise, mice accumulating intramyocellular triglycerides due to skeletal muscle-specific transgenic perilipin 5 overexpression also exhibit pronounced FGF21 expression in muscle and concomitantly increased circulating FGF21 concentrations (180). Also, human myopathy (mitochondrial and iron–sulfur cluster scaffold homolog (ISCU)) patients have higher expression of FGF21 in muscle and higher FGF21 serum levels (181) indicating some similarities between mice and men. It further indicates that under extreme metabolic disarrangements, muscle might contribute to circulating FGF21 levels in mice and humans.

G. Mitochondrial diseases

Mitochondrial diseases represent a heterogeneous group of rare genetic and acquired metabolic disorders characterized by mitochondrial dysfunction (for review, see (182)). Several groups demonstrated markedly elevated FGF21 blood levels in mitochondrial diseases (181,183–188). Although the molecular link is currently unclear, these findings are in line with increased FGF21 levels observed in common diseases associated with mitochondrial dysfunction, i.e., insulin resistance, non-alcoholic fatty liver disease, myopathy, and T2D (189–191).

H. Pancreatitis

One of the major FGF21 mRNA expression site in mice is pancreas. Pancreatic FGF21 gene expression derives from endocrine α- and β-cells as well as exocrine acinar cells (43,192–194). In the latter, FGF21 is induced in experimental models of pancreatitis in mice (43,193,194). In line, FGF21 is elevated in serum of patients with pancreatitis (195).

I. Lipodystrophies

Patients with human-immunodeficiency-virus-associated, congenital, and acquired lipodystrophies, i.e., pathologies characterized by reduced adipose tissue mass, marked ectopic lipid deposition, and insulin resistance demonstrate elevated FGF21 levels (196,197).

J. FGF21 resistance

With respect to FGF21's beneficial effects on murine glucose and lipid metabolism, the elevated FGF21 blood concentrations observed in murine and human diseases with disturbed glucose and lipid metabolism are completely unexpected. This has prompted the hypothesis of FGF21 resistance as it is comparable to high circulating insulin and leptin concentrations in insulin- and leptin-resistant states, respectively. Accordingly, treating diet-induced obese mice with recombinant human FGF21 leads to no significant decline in blood glucose concentrations and only a small decrease in plasma FFA concentrations together with attenuated ERK signaling and impaired induction of the FGF21 target genes Egr-1 and c-Fos in liver and adipose tissue (19,198). In line, human obesity is accompanied by elevated FGF21 levels and reduced levels of KLB in WAT (199). A recent study demonstrated impaired FGF21-induced ERK-phosphorylation in WAT of obese mice, which could not be restored by maintaining KLB expression in WAT indicating FGF21 resistance in WAT is downstream of KLB (200). Murine studies further indicate that thiazolidinediones may increase KLB expression thus potentially enhance FGF21 signaling (201) and recently it has been demonstrated that dietary fish oil increased hepatic FGF21 sensitivity by increasing KLB (202). However, there are also mouse studies arguing against FGF21 resistance: Hale *et al.* tested HFD-fed obese and genetically obese *ob/ob* mice (111) and found that even though WAT expression of β-Klotho and FGFR1c are reduced, dose-response curves with recombinant human FGF21 reveal no right-shifted ERK phosphorylation in liver or adipose tissue. Moreover these obese animals were more responsive to glucose- and weight-lowering

effects of FGF21 than lean mice (111). Whether these contradictory results derive from the different obesogenic diets or mouse strains used remains to be determined. More work is needed to prove or reject the hypothesis of FGF21 resistance in particular in human obesity and its associated metabolic complications.

In summary, any changes (physiological or pathophysiological) in metabolism (whole-body or just tissue-specific) are characterized by induction of FGF21 in mice and men. Thus, FGF21 emerge as an energy (nutritional) stress-induced factor not only in liver (Figure 2) but also in muscle, BAT/WAT, and pancreas (Figure 3). The contribution, however, of extrahepatic expression sites (adipose tissue and muscle) to circulating levels has only been suggested for some mouse models/conditions and direct data in humans are missing. Furthermore, it is not known how certain conditions provoke FGF21 release from the tissue into the circulation while others do not.

V. Metabolic effects of FGF21 in mice and men

A. Effects on whole-body glucose and lipid metabolism

Administration of (human or murine) recombinant FGF21 to nutritional (HFD-fed) or genetic (i.e., *ob*/*ob* and *db*/*db*) mouse models of obesity and diabetes increase fat utilization and energy expenditure, reduce body weight, whole-body fat mass, and liver triglyceride content (6,203,204). Furthermore, FGF21 administration provokes resistance to HFD-induced weight gain, improves glucose tolerance and hepatic and peripheral insulin sensitivity (without triggering hypoglycemia), and normalizes hyperinsulinemia and hypertriglyceridemia (6,203,204). *In vivo*, FGF21-mediated GLUT1 induction and glucose uptake in WAT is only seen in lean, but not in obese, mice suggesting that the robust reduction in blood glucose concentration observed in acutely FGF21-treated obese mouse models results from FGF21's indirect suppressive effect on hepatic glucose output (18,198,204). In the apolipoprotein (apo) E-deficient mouse model of atherosclerosis, FGF21 inhibits atherosclerotic plaque formation in part by suppressing hepatic expression of the transcription factor SREBP-2 thereby attenuating hepatic cholesterol synthesis and improving hypercholesterolemia (131). Conversely, whole-body FGF21 deficiency due to genetic knockout promotes weight gain, hepatosteatosis, and glucose intolerance upon ketogenic diet (64). The findings in mice about improvements in lipid- and glucose metabolism prompted pharma companies all over the world to develop FGF21-based novel therapies for metabolic diseases, especially for T2D.

Due to the instability of recombinant non-glycosylated FGF21 in the circulation, for humans only results with stabilized FGF21 analogues (LY2405319 and PF-05231023) are available (205–208). LY2405319 represents a human FGF21 molecule modified by introduction of an additional disulfide bond, deletion of four N-terminal amino acids, and elimination of an O-linked glycosylation site (209); PF-05231023 is an artificial macromolecule formed by covalent conjugation of two modified human FGF21 molecules (desHis FGF21 Ala129Cys) to the Fab regions of a monoclonal scaffold antibody (36). LY2405319 was already tested in T2D patients in a randomized placebo-controlled double-blind proof-of-concept trial (205): four weeks of LY2405319 treatment reduced plasma triglycerides, total and LDL cholesterol concentrations, increased plasma HDL cholesterol, β-hydroxybutyrate, and serum adiponectin concentrations, but did not reveal a significant effect on blood glucose levels. Similar effects on plasma lipids as well as a lack of effect on blood glucose were also observed for PF-05231023 after a single intravenous dose administered to T2D patients (206). Talukdar *et al.* performed a four-week randomized placebo-controlled phase-1b trial with twice-weekly administration of PF-05231023 (5-140 mg) in T2D patients and reported, apart from improvements in plasma lipids, significantly decreased body weight, increased blood adiponectin concentrations, reduced blood markers of bone formation,

increased markers of bone resorption, elevated blood IGF1 levels, and no effect on plasma glucose upon treatment (207). Another study using once-weekly injection of PF-05231023 (25-150 mg) in obese hypertriglyceridemic subjects reported reduced TG levels and increased adiponectin levels without changes in body weight, but again no improved glucose metabolism (208). It is unclear whether the observed weight loss in the study of Talukdar et al. are due to side effects, i.e., diarrhea and nausea (seen in 29 and 26 % of PF-05231023-treated patients, respectively) that may have impaired food intake (207). These human studies recapitulated the beneficial effects of FGF21 on lipid metabolism found in mouse studies, but revealed one crucial deviation: FGF21 analogues failed to lower blood glucose in humans. It has to be noted, however, that analogues (for overview of existing analogues see (210,211)) do not represent wild-type (regular) human FGF21. Therefore, it is currently unknown whether the reported effects of analogues reflect physiological functions of the endogenous protein.

B. Effects on growth and lifespan

FGF21 transgenic mice are markedly smaller than their wild-type littermates (212), and FGF21 causes hepatic GH resistance by blunting GH signaling at the extra- and intracellular level (212). Additionally, transgenic FGF21 overexpression extends lifespan of C57BL/6 mice by 36 % by interfering with GH/IGF1 signaling in liver without affecting food intake, physical activity, energy expenditure, or AMPK, mTOR, and Sirt signaling in liver, muscle, and adipose tissue (213). Recently, it has been demonstrated that an increase in lifespan by FGF21 overexpression involves the prevention of age-induced loss of naïve T cells (55). Given that these observations have been made with a mouse model that is hypermetabolic and growth-restricted due to transgenic overexpression of FGF21, an effect of FGF21 on lifespan and growth in humans is very speculative. A study investigating the association of FGF21 and growth or IGF-1 in obese children revealed no connection (116), contrasting another study demonstrating an inverse relationship of FGF21 with linear growth rate in infancy (214). Thus, FGF21 as a negative regulator of human growth has not been established, but awaits further studies.

C. Effects on glucose and lipid metabolism mediated by adipose tissue

As WAT has high FGFR1c and KLB expression and the FGFR1c/KLB complex is the preferred signaling complex for FGF21, adipose tissue is considered FGF21's major target. In HFD-fed mice, adipose tissue-selective ablation of either β-Klotho or FGFR1 impairs FGF21 effects, such as weight loss, insulin sensitization, and improvement of glucose tolerance, hyperinsulinemia, and hypertriglyceridemia (14,215,216). Additionally, the beneficial effects of FGF21 are absent in a mouse model of lipodystrophy but restored after WAT transplantation (217) indicating a central role for WAT in mediating FGF21 improvements on whole-body metabolism.

It has become clear that FGF21 plays a role in WAT lipolysis, but there are conflicting reports if FGF21 promotes or inhibits lipolysis. In particular, cell culture experiments using FGF21 treatment or gain- and loss-of-function studies in human or murine primary adipocytes or murine 3T3-L1 adipocytes, demonstrated inconsistent results (218–220). *In vivo* studies suggest a difference between chronic vs acute effects: Administration of a single dose of rhFGF21 acutely lowered plasma FFA concentrations and WAT HSL expression in lean and ob/ob mice (19,220). In contrast, mouse models with chronically altered FGF21 levels (knockout, overexpression and FGF21 administration) support the lipolysis-promoting effect of FGF21 with increased expression of lipases (HSL, ATGL), reduced adipocyte size, and elevated plasma FFA concentrations (45,64,221). This argues for a more indirect and context-depend effect of FGF21on WAT lipolysis which might also explain inconsistent cell culture results using different conditions. Recent mouse data indicate that inflammation (e.g.

mediated by IL6) might affect FGF21-mediated lipolysis (222) which is commonly observed in obesity and its associated metabolic disorders.

FGF21 acutely affects the production and release of the adipocyte-derived hormone (adipokine) adiponectin: a single FGF21 dose doubles adiponectin concentration in the blood (215). Adiponectin is an insulin-sensitizing, anti-inflammatory, and atheroprotective adipokine with a major role in glucose and lipid metabolism (223,224). When adiponectin is genetically ablated, HFD-induced and genetic mouse models of obesity are refractory to FGF21-induced improvements in hyperglycemia, hypertriglyceridemia, hepatic and muscle insulin resistance, and hepatosteatosis (225,226). Of note, the protective function of FGF21 on vascular inflammation and atherosclerotic plaque formation in apoE-deficient mice is at least in part dependent on its adiponectin-elevating properties (131). In humans, administration of the FGF21 analogue LY2405319 or PF-05231023 led to increased adiponectin levels in obese/diabetic patients (205,207,208) indicating that also human metabolism might benefit indirectly from FGF21 administration by increased adiponectin levels.

FGF21 stimulates glucose uptake in murine and human adipocytes (6) and Ge *et al.* demonstrated that this is due to transcriptional activation of the GLUT1 gene via ERK1/2, serum response factor, and Ets-like protein-1 (198). FGF21 effects on glucose uptake are more pronounced in BAT: *in vivo*, injecting native FGF21 into diet-induced obese mice increased glucose uptake in WAT but to a much higher extent in BAT (227,228), and mice having no circulating FGF21 (liver-specific FGF21 KO mice) show reduced glucose uptake specifically in BAT, not WAT, muscle or heart (42).

Schlein *et al.* reported that WAT and BAT contribute to FGF21-stimulated reductions in plasma triglyceride concentrations by enhanced clearance of triglyceride-rich lipoproteins in these depots (229). Additionally, Coskun *et al.* reported that chronic FGF21 administration in obese mouse models (HFD-fed and *ob*/*ob* mice) reduces body weight and adiposity via increased energy expenditure and fat utilization, suggesting the involvement of BAT (and/or browning of WAT) in these fat mass-regulating FGF21 effects (203). Adipose tissue browning (conversion of white adipocytes into brown-like UCP1-positive cells (230)) depends, at least in part, on FGF21 as FGF21-deficient mice display significantly diminished browning capacity (98). Furthermore, chronic FGF21 treatment and FGF21 gene transfer to the mouse liver are accompanied by induction of thermogenic genes (e.g. uncoupling protein 1 (UCP1)) and of genes favoring β-oxidation of fatty acids (e.g. CPT-1α and -1β) in BAT (52,203,231). Finally, induced hepatic FGF21 production may also be involved in activation of thermogenesis during the fetal-to-neonatal transition, a critical period where newborns have to compensate a dramatic drop in ambient temperature (47). There is uncertainty whether FGF21-induced adipose tissue browning is exclusively a direct effect on adipocytes: recent evidence, based on central β-Klotho knockout and lateral ventricle infusion of FGF21, suggests that hypothalamic FGF21 signaling stimulating sympathetic nerve activity contributes to adipose tissue browning (232,233). Of note, two reports support the notion that pharmacological FGF21 effects are independent of WAT browning (234,235). Although there seems to be a connection between FGF21 and BAT in humans as well (236), the rather low capacity for browning and the low amount of BAT in humans (usually at thermoneutrality) as compared with mice (commonly housed not at thermoneutrality) might explain at least partly the differences of FGF21's effects on glucose metabolism between the two species.

D. Effects on glucose and lipid metabolism mediated by liver

Among the earliest findings about FGF21 effects in mice was the stimulation of hepatic fatty acid oxidation (via induction of PGC-1α and -1β) and ketogenesis (via induction of ketone body-synthesizing enzymes) in the fasting state and under fasting state-mimicking conditions

(ketogenic diets) (29,45). Additionally, FGF21 suppresses hepatic *de novo* lipogenesis (via repression of the lipogenic genes encoding sterol regulatory element binding protein [SREBP] 1c and fatty acid synthase [FAS]) (29,237,238). Thus, FGF21 transgenic mice display decreased hepatic triglyceride contents (45) and FGF21 KO mice store fatty acids from fasting-associated adipose tissue lipolysis as triglycerides in the liver (29,64).

Chronic FGF21 treatment led to increased Akt phosphorylation, decreased diacylglycerol concentrations, and reduced protein kinase Cε activity in liver specimens indicating insulin sensitization at the hepatocellular level (237,239). In line, FGF21 KO mice demonstrate hepatic insulin resistance and elevated hepatic glucose production (240). Data obtained from liver-specific insulin receptor knockout (LIRKO) mice demonstrate that FGF21 effects on glucose metabolism are not due to direct effects on liver but to activation of BAT and browning of WAT, leading to increased energy metabolism and substrate use (85). These data further suggest that insulin action in the liver is not required for FGF21 to correct hyperglycemia but to mediate its effect on lipid metabolism in diabetic mice (85).

Berglund *et al.* and Xu *et al.* demonstrated that chronic FGF21 treatment suppressed hepatic glucose output and enhanced hepatic glycogen storage (18,204). By contrast, transgenic FGF21 mice demonstrated enhanced gluconeogenesis already during the fed state, and acute FGF21 treatment leads to PGC-1α-independent induction of the key gluconeogenic enzymes glucose-6-phosphatase and phosphoenol pyruvate carboxykinase, reflecting FGF21's prominent role during fasting (20,241).

However, a direct effect of FGF21 on liver *in vivo* has been questioned as FGFR4 being the main FGF receptor isoform expressed in liver and FGF21 does not activate down-stream signaling through the FGFR4/KLB-complex (no phosphorylation of ERK) (10). Besides indirect effects of FGF21 on liver, another explanation for a more direct FGF21 effect on liver has recently been proposed: FGF21 antagonizes the effect of FGF15/19 on hepatic FGFR4/KLB complex thereby increasing the bile acid pool (242). Several reports on FGF21 effects on human liver used HepG2 cells as a model for hepatocytes, but in contrast to primary hepatocytes, HepG2 cells do express high amounts of FGFR1c, therefore these data cannot be extrapolated into the human in vivo context. Nevertheless, human and murine liver do express FGFR1c, although to a much lower degree than adipose tissue, and hepatic FGFR3c expression is even higher than in adipose tissue (243). Notably, the regulating effect of FGF21 on cholesterol metabolisms has been suggested to be at least partly mediated via FGFR2-KLB complex in the liver (131), and FGFR2 is the second most abundant FGFR isoform in liver (10).

E. Effects on pancreas

Pancreatic acinar and islet cells are FGF21 targets, and FGF21 treatment triggers ERK signaling in both cell types (51). Wente *et al.* demonstrated that short-term FGF21 treatment of healthy C57BL/6 mice and diabetic *db/db* mice lowers blood insulin concentrations after an oral glucose load (244). By contrast, constant long-term infusion of FGF21 in *db/db* mice raises insulin (244). In the absence of enhanced islet cell proliferation, long-term treatment provokes increments in pancreatic islet number and insulin content per islet (244). On the other hand, FGF21 knockout mice display distortion of islet morphology and impaired glucose-stimulated insulin secretion, the latter possibly due to unblocked GH signaling in the islets (245). Moreover, HFD-fed FGF21-deficient mice develop islet hyperplasia and periductal lymphocytic inflammation (51). Notably, FGF21 has recently been discovered as a pancreatic secretagogue which mainly functions in an autocrine/paracrine manner to alleviate ER stress that can occur in pancreas under either physiological conditions such as fasting/refeeding or pathological conditions such as pancreatitis (43). Altogether, these findings point to islet-protective functions of FGF21. Interestingly, hyperglycemia in *db/db* mice and high glucose concentrations *in vitro* down-regulate β-Klotho expression and FGF21

signaling in pancreatic islets providing preliminary evidence of hyperglycemia-induced FGF21 resistance in the pancreas of diabetic mice (246). No published in vivo data on FGF21 expression or direct action on human pancreas are available.

F. Effects on brain

Very recently, it was demonstrated that FGF21 is expressed in different murine brain regions, including substantia nigra and striatum (247), and in cerebellar neurons upon treatment with cell adhesion molecule L1 (248). FGF21 expression in the brain in mice and most importantly in humans still needs further confirmation, and so far nothing is known about potential regulatory stimuli or mechanisms. Notably, however, FGF21 is able to pass the murine blood-brain barrier (249) and this seems to be true also for humans (250). In the brain of C57BL/6 mice, FGFR1c and FGFR3c, the two major FGFRs, are broadly expressed, whereas β-Klotho expression is restricted to the suprachiasmatic nucleus of the hypothalamus (SCN), where the circadian pacemaker is located, and the dorsal vagal complex (DVC) and nodose ganglia of the hindbrain (251). FGF21 action in the murine brain via β-Klotho increases corticosterone levels, lowers insulin levels, inhibits growth and alters circadian rhythm all representing features of starvation (251,252). Additionally, central FGF21 action is needed for its effect on energy expenditure (via WAT browning), weight loss and lowering cholesterol in mouse models (232,233,251,252). Using FGF21 knockout and intracerebroventricular FGF21 injection, Liang *et al.* demonstrated that acute stimulation of hepatic gluconeogenesis by FGF21, at least in part, is caused by FGF21's activation of the HPA axis triggering adrenal corticosterone release (via ERK-CREB-induced CRH gene expression in hypothalamic neurons) (252). Another central action of FGF21 has very recently been demonstrated in a mouse study: FGF21 suppressed consumption of simple sugars and non-caloric sweeteners, but not of complex carbohydrates, proteins, or lipids via hypothalamic neurons (59). Human genetic data (c.f. section V) point towards the existence of similar mechanisms in humans (62). These observations constitute a novel and multifunctional liver-brain axis with the hepatokine FGF21 as a crucial player in mice and men. Some controversial reports about actions of FGF21 in mice and men may be attributable to central effects as it has not been shown for FGF21 analogues if or how efficient they cross the blood-brain barrier. Additionally, although there are indications of KLB, FGFR1 and FGFR3 expression in human brain (c.f. proteinatlas.org), restricted expression to specific areas within the hypothalamus for instance, has not been demonstrated so far.

G. Effects on bone

The negative regulation of bones by FGF21 is one of the adverse effects which may jeopardize the use of FGF21 as a therapeutic (69,172). Even though the presence of β-Klotho in osteoblasts and/or osteoclasts remains to be proven, FGF21 has effects on bones: using transgenic overexpression and pharmacological application of FGF21, Wei *et al.* reported striking decreases in bone mass together with *ex vivo* assay data demonstrating inhibition of osteoblastogenesis and stimulation of adipogenesis in bone marrow-derived mesenchymal stem cells by FGF21 (172). By contrast, FGF21 KO mice exhibit a high-bone-mass phenotype (172) and are protected from transient loss of bone mass during lactation (253). Even though FGF21 has no direct impact on osteoclasts, it promotes IGFBP1 release from liver, and IGFBP1 stimulates bone resorption *in vivo* (254). Thus, FGF21 promotes bone loss via direct inhibition of bone formation and indirect enhancement of bone resorption. In humans, the FGF21 analogue PF-05231023 leads to changes in bone biomarkers with body weight changes (207) but also without body weight changes (208). Thus, adverse effects on bones need to be carefully addressed in future human studies.

Figure 4 summarizes effects (chronic and acute) of regular, i.e., wild-type, FGF21 on metabolically relevant tissues/organs in mice and humans as derived from treatment studies

and, for mice, from genetic manipulation as well: in brief, very similar FGF21 effects on lipid and glucose metabolism are reported in the two species with respect to adipocyte glucose uptake and mitochondrial oxidative capacity, fat cell browning, as well as hepatic fatty acid oxidation and *de novo* lipogenesis. On the other hand, obvious differences exist between mice and humans when looking closer at FGF21's effects on adipocyte lipolysis and hepatic ketogenesis. BAT seems to be the major tissue mediating FGF21 effects on glucose uptake and this might represent the reason for the missing effect of FGF21 on glucose in obese patients, which have only low or even no BAT (255,256).

VI. Human genetic data

In line with a potential role of FGFR2-KLB signaling in liver being responsible for FGF21 effects on cholesterol metabolism (131), a genetic variant of *FGFR2* (SNP rs2071616) is associated with LDL-C in humans (255). Consistent with a potential role of FGF21 in the brain, as proposed by mouse data, two large genome-wide association studies provided evidence that single nucleotide polymorphisms (SNPs) in or near the human FGF21 gene modulate macronutrient intake in humans independently of BMI: minor allele carriers of the synonymous SNP rs838133 in exon 1 of the FGF21 gene exhibit reduced energy intake from protein and increased energy intake from carbohydrates (256); and the minor allele of SNP rs838145, about 10 kb upstream of the FGF21 gene and in moderate linkage disequilibrium with rs838133 (r^2=0.7), is associated with higher energy intake from carbohydrates, lower energy intake from fat, and higher circulating FGF21 concentrations (257). The SNP rs838133 has recently been associated not only with sugar preference but also with more consumption of alcohol and tobacco, thus other forms of reward-seeking behavior. Interestingly, variations in KLB, the obligate FGF21 co-receptor have also been identified to be associated with alcohol drinking in humans (258). Even though functional data on how the SNPs alter FGF21 function/expression are lacking, these data suggest that genetic variation in the FGF21 gene and its receptor determines nutrient choices in humans by acting on the reward system.

VII. Summary and Conclusions

FGF21 represents a fascinating hormone with impressive implications in whole-body homeostasis and several metabolically relevant pathways in particular in lipid and glucose metabolism in both mice and men. This is why most work hitherto published was primarily driven by pharmacological interests and not by academic interests in this hormone's role in physiology and pathophysiology. Since 2000, the year of its discovery, FGF21 has been intensely studied in mice, and a wealth of very robust data has been generated in mice that, with the exception of a negative impact on bone metabolism, consistently document favorable roles of FGF21 in lipid and glucose metabolism. The last ten years of *in vivo* and *ex vivo* analyses in humans have also created a considerable body of data complicating the translation of several of the mouse findings to the human situation. Human treatment studies assessing the systemic effects of regular FGF21 are currently lacking due to the instability of recombinant non-glycosylated FGF21 in the circulation, but results from three treatment studies using FGF21 analogues are available (205–207). These studies revealed one crucial deviation from what is seen in mice: FGF21 analogues failed to lower blood glucose, and this is the reason why all pharmaceutical companies engaged in the development of FGF21-based anti-diabetic drugs (such as FGF21 analogues and activating anti-FGFR1c/β-Klotho antibodies, for review (210,211)) have now stopped their programs.

Based upon all what is hitherto known about FGF21, it is insufficient to explain the observed discrepancies of the pharmacological effect of FGF21 analogues on blood glucose

between mice and humans merely by limited availability of human data or by the ultimately unproven existence of FGF21 resistance. Rather, it is more obvious that the differences have species-specific reasons and derive from technical limitations associated with the use of mice as model organism for human physiology and disease. As species-inherent limitations, divergences due to adaptations of mice and humans to their specific habitats, dietary habits, and environmental constraints are conceivable. With regard to metabolism, it is well known that mice considerably differ from humans in lipoprotein metabolism and susceptibility to atherosclerosis (259) as well as in inflammatory responses to different traumata (260). A possible technical limitation of mouse studies may arise from housing temperatures that exert dramatic effects on inflammatory and atherosclerotic events (261) and BAT/WAT biology. As BAT and WAT are major targets of FGF21's beneficial effects on metabolism, we assume that this is the reason for the divergent findings between mice and men in particular on glucose metabolism. In line, it has been shown in a mouse model that FGF21's glucose lowering effect is blunted when KLB is specifically ablated in UCP^{+}-cells (262). There is no beneficial effect of FGF21 on glucose clearance in UCP1-deficient mice (263), and UCP1 KO mice treated with FGF21-Fc (another long-acting FGF21 analogue) demonstrated no reduction in plasma glucose (234). The relative small and varying amount of $UCP1^{+}$-cells in humans may explain the divergent effect of FGF21 on glucose metabolism in mice and men.

We have to stress that the vast majority of human *in vivo* data is of correlational nature. If correctly adjusted for known confounders, these data can help unmask real relationships. However, we have to admit that correlational data cannot give mechanistic insights or solve the problem of causation/reverse causation (the 'hen and egg' problem) inherent to all association analyses. In addition, only very few FGF21 treatment studies that harbor the potential to provide mechanistic clues are hitherto reported in humans. Apart from these limitations, an interesting observation is the robust positive correlation of FGF21 levels with many human metabolic disorders and diseases, e.g., metabolically unhealthy obesity, non-alcoholic hepatosteatosis, gestational diabetes, and T2D, coronary artery/heart disease, preeclampsia, myopathy, lipodystrophy and mitochondrial disease. Although, FGF21 as an anti-diabetic drug may not be feasible in humans, FGF21 might be a good biomarker and/or predictor for muscle-related mitochondrial diseases (183,264) or arteriosclerosis (265).

We should not abandon to further explore FGF21's biology, but follow-up investigations are required to ultimately solve the FGF21 puzzle. Given FGF21's prominent role in lipid metabolism in mice and men, patients suffering from metabolic disorders other than diabetes such as atherosclerosis might benefit from FGF21 therapies (131). But future studies need to carefully address issues such as the kind (e.g., murine versus human recombinant FGF21), dose and timing of FGF21 treatment. Maybe, new animal models closer to humans, e.g., omnivores like (mini)pigs, will provide functional and mechanistic data that can better be translated to the human situation. With respect to the emerging role of the brain in metabolic diseases (266–268), one of the most exciting and also most challenging areas of future research is certainly the assessment of the efficacy of FGF21 and its analogous in the brain.

Corresponding author and person to whom reprint requests should be addressed: Prof. Dr. Harald Staiger, Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Centre Munich at the University of Tübingen, Otfried-Müller-Str. 10, D-72076 Tübingen, Germany, Phone: +49-7071-29-85774, Fax: +49-7071-29-5646, E-mail: harald.staiger@med.uni-tuebingen.de

Disclosure statement: The authors have nothing to disclose.

References

1. **Cersosimo E, Triplitt C, Mandarino LJ, DeFronzo RA.** Pathogenesis of Type 2 Diabetes Mellitus. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, eds. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000.
2. **Kahn SE, Cooper ME, Del Prato S.** Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *The Lancet* 2014;383(9922):1068–1083.
3. **Fasshauer M, Blüher M.** Adipokines in health and disease. *Trends Pharmacol. Sci.* 2015;36(7):461–470.
4. **Pedersen BK.** Exercise-induced myokines and their role in chronic diseases. *Brain. Behav. Immun.* 2011;25(5):811–816.
5. **Stefan N, Häring H-U.** The role of hepatokines in metabolism. *Nat. Rev. Endocrinol.* 2013;9(3):144–152.
6. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, Sandusky GE, Hammond LJ, Moyers JS, Owens RA, Gromada J, Brozinick JT, Hawkins ED, Wroblewski VJ, Li D-S, Mehrbod F, Jaskunas SR, Shanafelt AB. FGF-21 as a novel metabolic regulator. *J. Clin. Invest.* 2005;115(6):1627–1635.
7. **Nishimura T, Nakatake Y, Konishi M, Itoh N.** Identification of a novel FGF, FGF-21, preferentially expressed in the liver1. *Biochim. Biophys. Acta BBA - Gene Struct. Expr.* 2000;1492(1):203–206.
8. **Oulion S, Bertrand S, Escriva H.** Evolution of the FGF Gene Family. *Int. J. Evol. Biol.* 2012;2012:1–12.
9. Goetz R, Beenken A, Ibrahimi OA, Kalinina J, Olsen SK, Eliseenkova AV, Xu C, Neubert TA, Zhang F, Linhardt RJ, Yu X, White KE, Inagaki T, Kliewer SA, Yamamoto M, Kurosu H, Ogawa Y, Kuro-o M, Lanske B, Razzaque MS, Mohammadi M. Molecular Insights into the Klotho-Dependent, Endocrine Mode of Action of Fibroblast Growth Factor 19 Subfamily Members. *Mol. Cell. Biol.* 2007;27(9):3417–3428.
10. **Kurosu H, Choi M, Ogawa Y, Dickson AS, Goetz R, Eliseenkova AV, Mohammadi M, Rosenblatt KP, Kliewer SA, Kuro-o M.** Tissue-specific expression of betaKlotho and fibroblast growth factor (FGF) receptor isoforms determines metabolic activity of FGF19 and FGF21. *J. Biol. Chem.* 2007;282(37):26687–26695.
11. **Ogawa Y, Kurosu H, Yamamoto M, Nandi A, Rosenblatt KP, Goetz R, Eliseenkova AV, Mohammadi M, Kuro-o M.** BetaKlotho is required for metabolic activity of fibroblast growth factor 21. *Proc. Natl. Acad. Sci. U. S. A.* 2007;104(18):7432–7437.
12. Kharitonenkov A, Dunbar JD, Bina HA, Bright S, Moyers JS, Zhang C, Ding L, Micanovic R, Mehrbod SF, Knierman MD, Hale JE, Coskun T, Shanafelt AB. FGF-21/FGF-21 receptor interaction and activation is determined by betaKlotho. *J. Cell. Physiol.* 2008;215(1):1–7.
13. **Suzuki M, Uehara Y, Motomura-Matsuzaka K, Oki J, Koyama Y, Kimura M, Asada M, Komi-Kuramochi A, Oka S, Imamura T.** betaKlotho is required for fibroblast growth factor (FGF) 21 signaling through FGF receptor (FGFR) 1c and FGFR3c. *Mol. Endocrinol. Baltim. Md* 2008;22(4):1006–1014.
14. **Ding X, Boney-Montoya J, Owen BM, Bookout AL, Coate KC, Mangelsdorf DJ, Kliewer SA.** βKlotho is required for fibroblast growth factor 21 effects on growth and metabolism. *Cell Metab.* 2012;16(3):387–393.
15. **Adams AC, Cheng CC, Coskun T, Kharitonenkov A.** FGF21 Requires βklotho to Act In Vivo. *PLoS ONE* 2012;7(11).
16. **Zhang X, Ibrahimi OA, Olsen SK, Umemori H, Mohammadi M, Ornitz DM.** Receptor Specificity of the Fibroblast Growth Factor Family THE COMPLETE MAMMALIAN FGF FAMILY. *J. Biol. Chem.* 2006;281(23):15694–15700.

17. **Ornitz DM, Itoh N.** The Fibroblast Growth Factor signaling pathway. *Wiley Interdiscip. Rev. Dev. Biol.* 2015;4(3):215–266.
18. Xu J, Stanislaus S, Chinookoswong N, Lau YY, Hager T, Patel J, Ge H, Weiszmann J, Lu S-C, Graham M, Busby J, Hecht R, Li Y-S, Li Y, Lindberg R, Véniant MM. Acute glucose-lowering and insulin-sensitizing action of FGF21 in insulin-resistant mouse models--association with liver and adipose tissue effects. *Am. J. Physiol. Endocrinol. Metab.* 2009;297(5):E1105-1114.
19. **Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonenkov A, Flier JS, Maratos-Flier E.** Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. *Diabetes* 2010;59(11):2781–2789.
20. **Fisher FM, Estall JL, Adams AC, Antonellis PJ, Bina HA, Flier JS, Kharitonenkov A, Spiegelman BM, Maratos-Flier E.** Integrated regulation of hepatic metabolism by fibroblast growth factor 21 (FGF21) in vivo. *Endocrinology* 2011;152(8):2996–3004.
21. **Moyers JS, Shiyanova TL, Mehrbod F, Dunbar JD, Noblitt TW, Otto KA, Reifel-Miller A, Kharitonenkov A.** Molecular determinants of FGF-21 activity-synergy and cross-talk with PPARgamma signaling. *J. Cell. Physiol.* 2007;210(1):1–6.
22. **Yang C, Jin C, Li X, Wang F, McKeehan WL, Luo Y.** Differential specificity of endocrine FGF19 and FGF21 to FGFR1 and FGFR4 in complex with KLB. *PloS One* 2012;7(3):e33870.
23. **Fon Tacer K, Bookout AL, Ding X, Kurosu H, John GB, Wang L, Goetz R, Mohammadi M, Kuro-o M, Mangelsdorf DJ, Kliewer SA.** Research Resource: Comprehensive Expression Atlas of the Fibroblast Growth Factor System in Adult Mouse. *Mol. Endocrinol.* 2010;24(10):2050–2064.
24. Petryszak R, Keays M, Tang YA, Fonseca NA, Barrera E, Burdett T, Füllgrabe A, Fuentes AM-P, Jupp S, Koskinen S, Mannion O, Huerta L, Megy K, Snow C, Williams E, Barzine M, Hastings E, Weisser H, Wright J, Jaiswal P, Huber W, Choudhary J, Parkinson HE, Brazma A. Expression Atlas update—an integrated database of gene and protein expression in humans, animals and plants. *Nucleic Acids Res.* 2016;44:D746–D752.
25. **Kharitonenkov A, Adams AC.** Inventing new medicines: The FGF21 story. *Mol. Metab.* 2013;3(3):221–229.
26. **Ito S, Kinoshita S, Shiraishi N, Nakagawa S, Sekine S, Fujimori T, Nabeshima YI.** Molecular cloning and expression analyses of mouse betaklotho, which encodes a novel Klotho family protein. *Mech. Dev.* 2000;98(1–2):115–119.
27. **Dutchak PA, Katafuchi T, Bookout AL, Choi JH, Yu RT, Mangelsdorf DJ, Kliewer SA.** Fibroblast growth factor-21 regulates PPARγ activity and the antidiabetic actions of thiazolidinediones. *Cell* 2012;148(3):556–567.
28. **Murata Y, Nishio K, Mochiyama T, Konishi M, Shimada M, Ohta H, Itoh N.** Fgf21 impairs adipocyte insulin sensitivity in mice fed a low-carbohydrate, high-fat ketogenic diet. *PloS One* 2013;8(7):e69330.
29. **Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E.** Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. *Cell Metab.* 2007;5(6):426–437.
30. **Gälman C, Lundåsen T, Kharitonenkov A, Bina HA, Eriksson M, Hafström I, Dahlin M, Amark P, Angelin B, Rudling M.** The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARalpha activation in man. *Cell Metab.* 2008;8(2):169–174.
31. Fazeli PK, Lun M, Kim SM, Bredella MA, Wright S, Zhang Y, Lee H, Catana C, Klibanski A, Patwari P, Steinhauser ML. FGF21 and the late adaptive response to starvation in humans. *J. Clin. Invest.* 2015;125(12):4601–4611.

32. **Zhang X, Yeung DCY, Karpisek M, Stejskal D, Zhou Z-G, Liu F, Wong RLC, Chow W-S, Tso AWK, Lam KSL, Xu A.** Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes* 2008;57(5):1246–1253.
33. **Dushay J, Chui PC, Gopalakrishnan GS, Varela-Rey M, Crawley M, Fisher FM, Badman MK, Martinez-Chantar ML, Maratos-Flier E.** Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. *Gastroenterology* 2010;139(2):456–463.
34. **Li H, Bao Y, Xu A, Pan X, Lu J, Wu H, Lu H, Xiang K, Jia W.** Serum fibroblast growth factor 21 is associated with adverse lipid profiles and gamma-glutamyltransferase but not insulin sensitivity in Chinese subjects. *J. Clin. Endocrinol. Metab.* 2009;94(6):2151–2156.
35. **Kharitonenkov A, Wroblewski VJ, Koester A, Chen Y-F, Clutinger CK, Tigno XT, Hansen BC, Shanafelt AB, Etgen GJ.** The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. *Endocrinology* 2007;148(2):774–781.
36. Huang J, Ishino T, Chen G, Rolzin P, Osothprarop TF, Retting K, Li L, Jin P, Matin MJ, Huyghe B, Talukdar S, Bradshaw CW, Palanki M, Violand BN, Woodnutt G, Lappe RW, Ogilvie K, Levin N. Development of a novel long-acting antidiabetic FGF21 mimetic by targeted conjugation to a scaffold antibody. *J. Pharmacol. Exp. Ther.* 2013;346(2):270–280.
37. Mu J, Pinkstaff J, Li Z, Skidmore L, Li N, Myler H, Dallas-Yang Q, Putnam A-M, Yao J, Bussell S, Wu M, Norman TC, Rodriguez CG, Kimmel B, Metzger JM, Manibusan A, Lee D, Zaller DM, Zhang BB, DiMarchi RD, Berger JP, Axelrod DW. FGF21 Analogs of Sustained Action Enabled by Orthogonal Biosynthesis Demonstrate Enhanced Antidiabetic Pharmacology in Rodents. *Diabetes* 2012;61(2):505–512.
38. **Zhen EY, Jin Z, Ackermann BL, Thomas MK, Gutierrez JA.** Circulating FGF21 proteolytic processing mediated by fibroblast activation protein. *Biochem. J.* 2016;473(Pt 5):605–614.
39. Dunshee DR, Bainbridge TW, Kljavin NM, Zavala-Solorio J, Schroeder AC, Chan R, Corpuz R, Wong M, Zhou W, Deshmukh G, Ly J, Sutherlin DP, Ernst JA, Sonoda J. Fibroblast Activation Protein Cleaves and Inactivates Fibroblast Growth Factor 21. *J. Biol. Chem.* 2016;291(11):5986–5996.
40. Yie J, Hecht R, Patel J, Stevens J, Wang W, Hawkins N, Steavenson S, Smith S, Winters D, Fisher S, Cai L, Belouski E, Chen C, Michaels ML, Li Y-S, Lindberg R, Wang M, Véniant M, Xu J. FGF21 N- and C-termini play different roles in receptor interaction and activation. *FEBS Lett.* 2009;583(1):19–24.
41. **Micanovic R, Raches DW, Dunbar JD, Driver DA, Bina HA, Dickinson CD, Kharitonenkov A.** Different roles of N- and C- termini in the functional activity of FGF21. *J. Cell. Physiol.* 2009;219(2):227–234.
42. **Markan KR, Naber MC, Ameka MK, Anderegg MD, Mangelsdorf DJ, Kliewer SA, Mohammadi M, Potthoff MJ.** Circulating FGF21 Is Liver Derived and Enhances Glucose Uptake During Refeeding and Overfeeding. *Diabetes* 2014;63(12):4057–4063.
43. Coate KC, Hernandez G, Thorne CA, Sun S, Le TDV, Vale K, Kliewer SA, Mangelsdorf DJ. FGF21 Is an Exocrine Pancreas Secretagogue. *Cell Metab.* 2017;25(2):472–480.
44. **Itoh N.** FGF21 as a Hepatokine, Adipokine, and Myokine in Metabolism and Diseases. *Front. Endocrinol.* 2014;5:107.
45. Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y, Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC, Hammer RE, Mangelsdorf DJ, Kliewer SA. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. *Cell Metab.* 2007;5(6):415–425.

46. **Lundåsen T, Hunt MC, Nilsson L-M, Sanyal S, Angelin B, Alexson SEH, Rudling M.** PPARalpha is a key regulator of hepatic FGF21. *Biochem. Biophys. Res. Commun.* 2007;360(2):437–440.
47. **Hondares E, Rosell M, Gonzalez FJ, Giralt M, Iglesias R, Villarroya F.** Hepatic FGF21 expression is induced at birth via PPARalpha in response to milk intake and contributes to thermogenic activation of neonatal brown fat. *Cell Metab.* 2010;11(3):206–212.
48. **Schmid A, Leszczak S, Ober I, Karrasch T, Schäffler A.** Short-term and divergent regulation of FGF-19 and FGF-21 during oral lipid tolerance test but not oral glucose tolerance test. *Exp. Clin. Endocrinol. Diabetes Off. J. Ger. Soc. Endocrinol. Ger. Diabetes Assoc.* 2015;123(2):88–94.
49. **Matikainen N, Taskinen M-R, Stennabb S, Lundbom N, Hakkarainen A, Vaaralahti K, Raivio T.** Decrease in circulating fibroblast growth factor 21 after an oral fat load is related to postprandial triglyceride-rich lipoproteins and liver fat. *Eur. J. Endocrinol.* 2012;166(3):487–492.
50. **Christodoulides C, Dyson P, Sprecher D, Tsintzas K, Karpe F.** Circulating fibroblast growth factor 21 is induced by peroxisome proliferator-activated receptor agonists but not ketosis in man. *J. Clin. Endocrinol. Metab.* 2009;94(9):3594–3601.
51. Singhal G, Fisher ffolliott M, Chee MJ, Tan TG, Ouaamari AE, Adams AC, Najarian R, Kulkarni RN, Benoist C, Flier JS, Maratos-Flier E. Fibroblast Growth Factor 21 (FGF21) Protects against High Fat Diet Induced Inflammation and Islet Hyperplasia in Pancreas. *PloS One* 2016;11(2):e0148252.
52. **Muise ES, Azzolina B, Kuo DW, El-Sherbeini M, Tan Y, Yuan X, Mu J, Thompson JR, Berger JP, Wong KK.** Adipose fibroblast growth factor 21 is up-regulated by peroxisome proliferator-activated receptor gamma and altered metabolic states. *Mol. Pharmacol.* 2008;74(2):403–412.
53. **Izumiya Y, Bina HA, Ouchi N, Akasaki Y, Kharitonenkov A, Walsh K.** FGF21 is an Akt-regulated myokine. *FEBS Lett.* 2008;582(27):3805–3810.
54. **Jiang X, Zhang C, Xin Y, Huang Z, Tan Y, Huang Y, Wang Y, Feng W, Li X, Li W, Qu Y, Cai L.** Protective effect of FGF21 on type 1 diabetes-induced testicular apoptotic cell death probably via both mitochondrial- and endoplasmic reticulum stress-dependent pathways in the mouse model. *Toxicol. Lett.* 2013;219(1):65–76.
55. **Youm Y-H, Horvath TL, Mangelsdorf DJ, Kliewer SA, Dixit VD.** Prolongevity hormone FGF21 protects against immune senescence by delaying age-related thymic involution. *Proc. Natl. Acad. Sci.* 2016;113(4):1026–1031.
56. **Lundsgaard A-M, Fritzen AM, Sjøberg KA, Myrmel LS, Madsen L, Wojtaszewski JFP, Richter EA, Kiens B.** Circulating FGF21 in humans is potently induced by short term overfeeding of carbohydrates. *Mol. Metab.* 2016;6(1):22–29.
57. Solon-Biet SM, Cogger VC, Pulpitel T, Heblinski M, Wahl D, McMahon AC, Warren A, Durrant-Whyte J, Walters KA, Krycer JR, Ponton F, Gokarn R, Wali JA, Ruohonen K, Conigrave AD, James DE, Raubenheimer D, Morrison CD, Le Couteur DG, Simpson SJ. Defining the Nutritional and Metabolic Context of FGF21 Using the Geometric Framework. *Cell Metab.* 2016;24(4):555–565.
58. **Fisher FM, Kim M, Doridot L, Cunniff JC, Parker TS, Levine DM, Hellerstein MK, Hudgins LC, Maratos-Flier E, Herman MA.** A critical role for ChREBP-mediated FGF21 secretion in hepatic fructose metabolism. *Mol. Metab.* 2017;6(1):14–21.
59. von Holstein-Rathlou S, BonDurant LD, Peltekian L, Naber MC, Yin TC, Claflin KE, Urizar AI, Madsen AN, Ratner C, Holst B, Karstoft K, Vandenbeuch A, Anderson CB, Cassell MD, Thompson AP, Solomon TP, Rahmouni K, Kinnamon SC, Pieper AA, Gillum

MP, Potthoff MJ. FGF21 Mediates Endocrine Control of Simple Sugar Intake and Sweet Taste Preference by the Liver. *Cell Metab.* 2016;23(2):335–343.
60. **Dushay JR, Toschi E, Mitten EK, Fisher FM, Herman MA, Maratos-Flier E.** Fructose ingestion acutely stimulates circulating FGF21 levels in humans. *Mol. Metab.* 2015;4(1):51–57.
61. Talukdar S, Owen BM, Song P, Hernandez G, Zhang Y, Zhou Y, Scott WT, Paratala B, Turner T, Smith A, Bernardo B, Müller CP, Tang H, Mangelsdorf DJ, Goodwin B, Kliewer SA. FGF21 Regulates Sweet and Alcohol Preference. *Cell Metab.* 2016;23(2):344–349.
62. Søberg S, Sandholt CH, Jespersen NZ, Toft U, Madsen AL, von Holstein-Rathlou S, Grevengoed TJ, Christensen KB, Bredie WLP, Potthoff MJ, Solomon TPJ, Scheele C, Linneberg A, Jørgensen T, Pedersen O, Hansen T, Gillum MP, Grarup N. FGF21 Is a Sugar-Induced Hormone Associated with Sweet Intake and Preference in Humans. *Cell Metab.* 2017;25(5):1045–1053.e6.
63. Crujeiras AB, Gomez-Arbelaez D, Zulet MA, Carreira MC, Sajoux I, de Luis D, Castro AI, Baltar J, Baamonde I, Sueiro A, Macias-Gonzalez M, Bellido D, Tinahones FJ, Martinez JA, Casanueva FF. Plasma FGF21 levels in obese patients undergoing energy-restricted diets or bariatric surgery: A marker of metabolic stress? *Int. J. Obes. 2005* 2017. doi:10.1038/ijo.2017.138.
64. **Badman MK, Koester A, Flier JS, Kharitonenkov A, Maratos-Flier E.** Fibroblast growth factor 21-deficient mice demonstrate impaired adaptation to ketosis. *Endocrinology* 2009;150(11):4931–4940.
65. **Asrih M, Altirriba J, Rohner-Jeanrenaud F, Jornayvaz FR.** Ketogenic Diet Impairs FGF21 Signaling and Promotes Differential Inflammatory Responses in the Liver and White Adipose Tissue. *PloS One* 2015;10(5):e0126364.
66. Laeger T, Henagan TM, Albarado DC, Redman LM, Bray GA, Noland RC, Münzberg H, Hutson SM, Gettys TW, Schwartz MW, Morrison CD. FGF21 is an endocrine signal of protein restriction. *J. Clin. Invest.* 2014;124(9):3913–3922.
67. **Pissios P, Hong S, Kennedy AR, Prasad D, Liu F-F, Maratos-Flier E.** Methionine and choline regulate the metabolic phenotype of a ketogenic diet. *Mol. Metab.* 2013;2(3):306–313.
68. **De Sousa-Coelho AL, Relat J, Hondares E, Pérez-Martí A, Ribas F, Villarroya F, Marrero PF, Haro D.** FGF21 mediates the lipid metabolism response to amino acid starvation. *J. Lipid Res.* 2013;54(7):1786–1797.
69. **Ables GP, Perrone CE, Orentreich D, Orentreich N.** Methionine-restricted C57BL/6J mice are resistant to diet-induced obesity and insulin resistance but have low bone density. *PloS One* 2012;7(12):e51357.
70. **Lees EK, Król E, Grant L, Shearer K, Wyse C, Moncur E, Bykowska AS, Mody N, Gettys TW, Delibegovic M.** Methionine restriction restores a younger metabolic phenotype in adult mice with alterations in fibroblast growth factor 21. *Aging Cell* 2014;13(5):817–827.
71. **De Sousa-Coelho AL, Marrero PF, Haro D.** Activating transcription factor 4-dependent induction of FGF21 during amino acid deprivation. *Biochem. J.* 2012;443(1):165–171.
72. Fontana L, Cummings NE, Arriola Apelo SI, Neuman JC, Kasza I, Schmidt BA, Cava E, Spelta F, Tosti V, Syed FA, Baar EL, Veronese N, Cottrell SE, Fenske RJ, Bertozzi B, Brar HK, Pietka T, Bullock AD, Figenshau RS, Andriole GL, Merrins MJ, Alexander CM, Kimple ME, Lamming DW. Decreased Consumption of Branched-Chain Amino Acids Improves Metabolic Health. *Cell Rep.* 2016;16(2):520–530.

73. **Kim KH, Kim SH, Min Y-K, Yang H-M, Lee J-B, Lee M-S.** Acute exercise induces FGF21 expression in mice and in healthy humans. *PloS One* 2013;8(5):e63517.
74. Cuevas-Ramos D, Almeda-Valdés P, Meza-Arana CE, Brito-Córdova G, Gómez-Pérez FJ, Mehta R, Oseguera-Moguel J, Aguilar-Salinas CA. Exercise increases serum fibroblast growth factor 21 (FGF21) levels. *PloS One* 2012;7(5):e38022.
75. **Slusher AL, Whitehurst M, Zoeller RF, Mock JT, Maharaj M, Huang C-J.** Attenuated fibroblast growth factor 21 response to acute aerobic exercise in obese individuals. *Nutr. Metab. Cardiovasc. Dis. NMCD* 2015;25(9):839–845.
76. **Hansen JS, Clemmesen JO, Secher NH, Hoene M, Drescher A, Weigert C, Pedersen BK, Plomgaard P.** Glucagon-to-insulin ratio is pivotal for splanchnic regulation of FGF-21 in humans. *Mol. Metab.* 2015;4(8):551–560.
77. **Hansen JS, Pedersen BK, Xu G, Lehmann R, Weigert C, Plomgaard P.** Exercise-Induced Secretion of FGF21 and Follistatin Are Blocked by Pancreatic Clamp and Impaired in Type 2 Diabetes. *J. Clin. Endocrinol. Metab.* 2016;101(7):2816–2825.
78. Habegger KM, Stemmer K, Cheng C, Müller TD, Heppner KM, Ottaway N, Holland J, Hembree JL, Smiley D, Gelfanov V, Krishna R, Arafat AM, Konkar A, Belli S, Kapps M, Woods SC, Hofmann SM, D'Alessio D, Pfluger PT, Perez-Tilve D, Seeley RJ, Konishi M, Itoh N, Kharitonenkov A, Spranger J, DiMarchi RD, Tschöp MH. Fibroblast growth factor 21 mediates specific glucagon actions. *Diabetes* 2013;62(5):1453–1463.
79. Arafat AM, Kaczmarek P, Skrzypski M, Pruszyńska-Oszmalek E, Kołodziejski P, Szczepankiewicz D, Sassek M, Wojciechowicz T, Wiedenmann B, Pfeiffer AFH, Nowak KW, Strowski MZ. Glucagon increases circulating fibroblast growth factor 21 independently of endogenous insulin levels: a novel mechanism of glucagon-stimulated lipolysis? *Diabetologia* 2013;56(3):588–597.
80. Mai K, Andres J, Biedasek K, Weicht J, Bobbert T, Sabath M, Meinus S, Reinecke F, Mohlig M, Weickert MO, Clemenz M, Pfeiffer AFH, Kintscher U, Spuler S, Spranger J. Free Fatty Acids Link Metabolism and Regulation of the Insulin-Sensitizing Fibroblast Growth Factor-21. *Diabetes* 2009;58(7):1532–1538.
81. **Mraz M, Bartlova M, Lacinova Z, Michalsky D, Kasalicky M, Haluzikova D, Matoulek M, Dostalova I, Humenanska V, Haluzik M.** Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. *Clin. Endocrinol. (Oxf.)* 2009;71(3):369–375.
82. **Hojman P, Pedersen M, Nielsen AR, Krogh-Madsen R, Yfanti C, Akerstrom T, Nielsen S, Pedersen BK.** Fibroblast growth factor-21 is induced in human skeletal muscles by hyperinsulinemia. *Diabetes* 2009;58(12):2797–2801.
83. **Vienberg SG, Brøns C, Nilsson E, Astrup A, Vaag A, Andersen B.** Impact of short-term high-fat feeding and insulin-stimulated FGF21 levels in subjects with low birth weight and controls. *Eur. J. Endocrinol.* 2012;167(1):49–57.
84. **Harris L-ALS, Smith GI, Patterson BW, Ramaswamy RS, Okunade A, Kelly SC, Porter LC, Klein S, Yoshino J, Mittendorfer B.** Alterations in 3-Hydroxyisobutyrate and FGF21 Metabolism are Associated with Protein Ingestion-Induced Insulin Resistance. *Diabetes* 2017. doi:10.2337/db16-1475.
85. **Emanuelli B, Vienberg SG, Smyth G, Cheng C, Stanford KI, Arumugam M, Michael MD, Adams AC, Kharitonenkov A, Kahn CR.** Interplay between FGF21 and insulin action in the liver regulates metabolism. *J. Clin. Invest.* 2014;124(2):515–527.
86. **Chen W, Hoo RL, Konishi M, Itoh N, Lee P-C, Ye H, Lam KS, Xu A.** Growth hormone induces hepatic production of fibroblast growth factor 21 through a mechanism dependent on lipolysis in adipocytes. *J. Biol. Chem.* 2011;286(40):34559–34566.

87. **Lundberg J, Höybye C, Krusenstjerna-Hafstrøm T, Bina HA, Kharitonenkov A, Angelin B, Rudling M.** Influence of growth hormone on circulating fibroblast growth factor 21 levels in humans. *J. Intern. Med.* 2013;274(3):227–232.
88. **Adams AC, Astapova I, Fisher FM, Badman MK, Kurgansky KE, Flier JS, Hollenberg AN, Maratos-Flier E.** Thyroid hormone regulates hepatic expression of fibroblast growth factor 21 in a PPARalpha-dependent manner. *J. Biol. Chem.* 2010;285(19):14078–14082.
89. **Domouzoglou EM, Fisher FM, Astapova I, Fox EC, Kharitonenkov A, Flier JS, Hollenberg AN, Maratos-Flier E.** Fibroblast growth factor 21 and thyroid hormone show mutual regulatory dependency but have independent actions in vivo. *Endocrinology* 2014;155(5):2031–2040.
90. **Patel R, Bookout AL, Magomedova L, Owen BM, Consiglio GP, Shimizu M, Zhang Y, Mangelsdorf DJ, Kliewer SA, Cummins CL.** Glucocorticoids regulate the metabolic hormone FGF21 in a feed-forward loop. *Mol. Endocrinol. Baltim. Md* 2015;29(2):213–223.
91. **Bonde Y, Breuer O, Lütjohann D, Sjöberg S, Angelin B, Rudling M.** Thyroid hormone reduces PCSK9 and stimulates bile acid synthesis in humans. *J. Lipid Res.* 2014;55(11):2408–2415.
92. **Tong X, Muchnik M, Chen Z, Patel M, Wu N, Joshi S, Rui L, Lazar MA, Yin L.** Transcriptional repressor E4-binding protein 4 (E4BP4) regulates metabolic hormone fibroblast growth factor 21 (FGF21) during circadian cycles and feeding. *J. Biol. Chem.* 2010;285(47):36401–36409.
93. **Oishi K, Uchida D, Ishida N.** Circadian expression of FGF21 is induced by PPARalpha activation in the mouse liver. *FEBS Lett.* 2008;582(25–26):3639–3642.
94. **Andersen B, Beck-Nielsen H, Højlund K.** Plasma FGF21 displays a circadian rhythm during a 72-h fast in healthy female volunteers. *Clin. Endocrinol. (Oxf.)* 2011;75(4):514–519.
95. **Wang Y, Solt LA, Burris TP.** Regulation of FGF21 expression and secretion by retinoic acid receptor-related orphan receptor alpha. *J. Biol. Chem.* 2010;285(21):15668–15673.
96. **Estall JL, Ruas JL, Choi CS, Laznik D, Badman M, Maratos-Flier E, Shulman GI, Spiegelman BM.** PGC-1alpha negatively regulates hepatic FGF21 expression by modulating the heme/Rev-Erb(alpha) axis. *Proc. Natl. Acad. Sci. U. S. A.* 2009;106(52):22510–22515.
97. **Yu H, Xia F, Lam KSL, Wang Y, Bao Y, Zhang J, Gu Y, Zhou P, Lu J, Jia W, Xu A.** Circadian rhythm of circulating fibroblast growth factor 21 is related to diurnal changes in fatty acids in humans. *Clin. Chem.* 2011;57(5):691–700.
98. Fisher ffolliott M, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdeguer F, Wu J, Kharitonenkov A, Flier JS, Maratos-Flier E, Spiegelman BM. FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. *Genes Dev.* 2012;26(3):271–281.
99. **Chartoumpekis DV, Habeos IG, Ziros PG, Psyrogiannis AI, Kyriazopoulou VE, Papavassiliou AG.** Brown adipose tissue responds to cold and adrenergic stimulation by induction of FGF21. *Mol. Med. Camb. Mass* 2011;17(7–8):736–740.
100. **Hondares E, Iglesias R, Giralt A, Gonzalez FJ, Giralt M, Mampel T, Villarroya F.** Thermogenic activation induces FGF21 expression and release in brown adipose tissue. *J. Biol. Chem.* 2011;286(15):12983–12990.
101. **Lee P, Brychta RJ, Linderman J, Smith S, Chen KY, Celi FS.** Mild cold exposure modulates fibroblast growth factor 21 (FGF21) diurnal rhythm in humans: relationship

between FGF21 levels, lipolysis, and cold-induced thermogenesis. *J. Clin. Endocrinol. Metab.* 2013;98(1):E98-102.
102. Lee P, Linderman JD, Smith S, Brychta RJ, Wang J, Idelson C, Perron RM, Werner CD, Phan GQ, Kammula US, Kebebew E, Pacak K, Chen KY, Celi FS. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. *Cell Metab.* 2014;19(2):302–309.
103. **Keipert S, Kutschke M, Lamp D, Brachthäuser L, Neff F, Meyer CW, Oelkrug R, Kharitonenkov A, Jastroch M.** Genetic disruption of uncoupling protein 1 in mice renders brown adipose tissue a significant source of FGF21 secretion. *Mol. Metab.* 2015;4(7):537–542.
104. **Eto K, Tumenbayar B, Nagashima S, Tazoe F, Miyamoto M, Takahashi M, Ando A, Okada K, Yagyu H, Ishibashi S.** Distinct association of serum FGF21 or adiponectin levels with clinical parameters in patients with type 2 diabetes. *Diabetes Res. Clin. Pract.* 2010;89(1):52–57.
105. **Ong KL, Rye K-A, O'Connell R, Jenkins AJ, Brown C, Xu A, Sullivan DR, Barter PJ, Keech AC, FIELD study investigators.** Long-term fenofibrate therapy increases fibroblast growth factor 21 and retinol-binding protein 4 in subjects with type 2 diabetes. *J. Clin. Endocrinol. Metab.* 2012;97(12):4701–4708.
106. **Cyphert HA, Ge X, Kohan AB, Salati LM, Zhang Y, Hillgartner FB.** Activation of the farnesoid X receptor induces hepatic expression and secretion of fibroblast growth factor 21. *J. Biol. Chem.* 2012;287(30):25123–25138.
107. **Li Y, Wong K, Walsh K, Gao B, Zang M.** Retinoic acid receptor β stimulates hepatic induction of fibroblast growth factor 21 to promote fatty acid oxidation and control whole-body energy homeostasis in mice. *J. Biol. Chem.* 2013;288(15):10490–10504.
108. **Bae K-H, Min A-K, Kim J-G, Lee I-K, Park K-G.** Alpha lipoic acid induces hepatic fibroblast growth factor 21 expression via up-regulation of CREBH. *Biochem. Biophys. Res. Commun.* 2014;455(3–4):212–217.
109. **Chen S, Zhao X, Ran L, Wan J, Wang X, Qin Y, Shu F, Gao Y, Yuan L, Zhang Q, Mi M.** Resveratrol improves insulin resistance, glucose and lipid metabolism in patients with non-alcoholic fatty liver disease: a randomized controlled trial. *Dig. Liver Dis. Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver* 2015;47(3):226–232.
110. **Li Y, Wong K, Giles A, Jiang J, Lee JW, Adams AC, Kharitonenkov A, Yang Q, Gao B, Guarente L, Zang M.** Hepatic SIRT1 Attenuates Hepatic Steatosis and Controls Energy Balance in Mice by Inducing Fibroblast Growth Factor 21. *Gastroenterology* 2014;146(2):539–549.e7.
111. **Hale C, Chen MM, Stanislaus S, Chinookoswong N, Hager T, Wang M, Véniant MM, Xu J.** Lack of overt FGF21 resistance in two mouse models of obesity and insulin resistance. *Endocrinology* 2012;153(1):69–80.
112. Cuevas-Ramos D, Almeda-Valdes P, Gómez-Pérez FJ, Meza-Arana CE, Cruz-Bautista I, Arellano-Campos O, Navarrete-López M, Aguilar-Salinas CA. Daily physical activity, fasting glucose, uric acid, and body mass index are independent factors associated with serum fibroblast growth factor 21 levels. *Eur. J. Endocrinol.* 2010;163(3):469–477.
113. **Lee Y, Lim S, Hong E-S, Kim JH, Moon MK, Chun EJ, Choi SI, Kim Y-B, Park YJ, Park KS, Jang HC, Choi SH.** Serum FGF21 concentration is associated with hypertriglyceridaemia, hyperinsulinaemia and pericardial fat accumulation, independently of obesity, but not with current coronary artery status. *Clin. Endocrinol. (Oxf.)* 2014;80(1):57–64.
114. **Akyildiz ZI, Polat S, Yurekli BS, Kocabas GU, Tuluce K, Tuluce SY, Kocabas U, Bozkaya G, Yuksel A, Nazli C.** Epicardial fat, body mass index, and triglyceride are

independent contributors of serum fibroblast growth factor 21 level in obese premenopausal women. *J. Endocrinol. Invest.* 2015;38(3):361–366.
115. **Taniguchi H, Tanisawa K, Sun X, Cao Z-B, Oshima S, Ise R, Sakamoto S, Higuchi M.** Cardiorespiratory fitness and visceral fat are key determinants of serum fibroblast growth factor 21 concentration in Japanese men. *J. Clin. Endocrinol. Metab.* 2014;99(10):E1877-1884.
116. **Reinehr T, Woelfle J, Wunsch R, Roth CL.** Fibroblast growth factor 21 (FGF-21) and its relation to obesity, metabolic syndrome, and nonalcoholic fatty liver in children: a longitudinal analysis. *J. Clin. Endocrinol. Metab.* 2012;97(6):2143–2150.
117. **Heilbronn LK, Campbell LV, Xu A, Samocha-Bonet D.** Metabolically protective cytokines adiponectin and fibroblast growth factor-21 are increased by acute overfeeding in healthy humans. *PloS One* 2013;8(10):e78864.
118. **Iggman D, Rosqvist F, Larsson A, Arnlöv J, Beckman L, Rudling M, Risérus U.** Role of dietary fats in modulating cardiometabolic risk during moderate weight gain: a randomized double-blind overfeeding trial (LIPOGAIN study). *J. Am. Heart Assoc.* 2014;3(5):e001095.
119. **Woelnerhanssen B, Peterli R, Steinert RE, Peters T, Borbély Y, Beglinger C.** Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy--a prospective randomized trial. *Surg. Obes. Relat. Dis. Off. J. Am. Soc. Bariatr. Surg.* 2011;7(5):561–568.
120. **Jansen PLM, van Werven J, Aarts E, Berends F, Janssen I, Stoker J, Schaap FG.** Alterations of hormonally active fibroblast growth factors after Roux-en-Y gastric bypass surgery. *Dig. Dis. Basel Switz.* 2011;29(1):48–51.
121. **Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, Balletshofer B, Machicao F, Fritsche A, Häring H-U.** Identification and characterization of metabolically benign obesity in humans. *Arch. Intern. Med.* 2008;168(15):1609–1616.
122. Böhm A, Halama A, Meile T, Zdichavsky M, Lehmann R, Weigert C, Fritsche A, Stefan N, Königsrainer A, Häring H-U, de Angelis MH, Adamski J, Staiger H. Metabolic signatures of cultured human adipocytes from metabolically healthy versus unhealthy obese individuals. *PloS One* 2014;9(4):e93148.
123. **Das SK, Ma L, Sharma NK.** Adipose tissue gene expression and metabolic health of obese adults. *Int. J. Obes. 2005* 2015;39(5):869–873.
124. **Hwang Y-C, Hayashi T, Fujimoto WY, Kahn SE, Leonetti DL, McNeely MJ, Boyko EJ.** Visceral abdominal fat accumulation predicts the conversion of metabolically healthy obese subjects to an unhealthy phenotype. *Int. J. Obes. 2005* 2015;39(9):1365–1370.
125. Berti L, Irmler M, Zdichavsky M, Meile T, Böhm A, Stefan N, Fritsche A, Beckers J, Königsrainer A, Häring H-U, de Angelis MH, Staiger H. Fibroblast growth factor 21 is elevated in metabolically unhealthy obesity and affects lipid deposition, adipogenesis, and adipokine secretion of human abdominal subcutaneous adipocytes. *Mol. Metab.* 2015;4(7):519–527.
126. **Cheng X, Zhu B, Jiang F, Fan H.** Serum FGF-21 levels in type 2 diabetic patients. *Endocr. Res.* 2011;36(4):142–148.
127. **Semba RD, Sun K, Egan JM, Crasto C, Carlson OD, Ferrucci L.** Relationship of serum fibroblast growth factor 21 with abnormal glucose metabolism and insulin resistance: the Baltimore Longitudinal Study of Aging. *J. Clin. Endocrinol. Metab.* 2012;97(4):1375–1382.
128. **Gaemers IC, Stallen JM, Kunne C, Wallner C, van Werven J, Nederveen A, Lamers WH.** Lipotoxicity and steatohepatitis in an overfed mouse model for non-alcoholic fatty liver disease. *Biochim. Biophys. Acta* 2011;1812(4):447–458.

129. **Jiang S, Yan C, Fang Q, Shao M, Zhang Y, Liu Y, Deng Y, Shan B, Liu J, Li H, Yang L, Zhou J, Dai Z, Liu Y, Jia W.** Fibroblast growth factor 21 is regulated by the IRE1α-XBP1 branch of the unfolded protein response and counteracts endoplasmic reticulum stress-induced hepatic steatosis. *J. Biol. Chem.* 2014;289(43):29751–29765.
130. **Wu X, Qi Y-F, Chang J-R, Lu W-W, Zhang J-S, Wang S-P, Cheng S-J, Zhang M, Fan Q, Lv Y, Zhu H, Xin M-K, Lv Y, Liu J-H.** Possible role of fibroblast growth factor 21 on atherosclerosis via amelioration of endoplasmic reticulum stress-mediated apoptosis in apoE(-/-) mice. *Heart Vessels* 2015;30(5):657–668.
131. **Lin Z, Pan X, Wu F, Ye D, Zhang Y, Wang Y, Jin L, Lian Q, Huang Y, Ding H, Triggle C, Wang K, Li X, Xu A.** Fibroblast growth factor 21 prevents atherosclerosis by suppression of hepatic sterol regulatory element-binding protein-2 and induction of adiponectin in mice. *Circulation* 2015;131(21):1861–1871.
132. **Bobbert T, Schwarz F, Fischer-Rosinsky A, Pfeiffer AFH, Möhlig M, Mai K, Spranger J.** Fibroblast growth factor 21 predicts the metabolic syndrome and type 2 diabetes in Caucasians. *Diabetes Care* 2013;36(1):145–149.
133. **Novotny D, Vaverkova H, Karasek D, Lukes J, Slavik L, Malina P, Orsag J.** Evaluation of total adiponectin, adipocyte fatty acid binding protein and fibroblast growth factor 21 levels in individuals with metabolic syndrome. *Physiol. Res.* 2014;63(2):219–228.
134. **Li H, Fang Q, Gao F, Fan J, Zhou J, Wang X, Zhang H, Pan X, Bao Y, Xiang K, Xu A, Jia W.** Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. *J. Hepatol.* 2010;53(5):934–940.
135. **Yan H, Xia M, Chang X, Xu Q, Bian H, Zeng M, Rao S, Yao X, Tu Y, Jia W, Gao X.** Circulating fibroblast growth factor 21 levels are closely associated with hepatic fat content: a cross-sectional study. *PloS One* 2011;6(9):e24895.
136. **Giannini C, Feldstein AE, Santoro N, Kim G, Kursawe R, Pierpont B, Caprio S.** Circulating levels of FGF-21 in obese youth: associations with liver fat content and markers of liver damage. *J. Clin. Endocrinol. Metab.* 2013;98(7):2993–3000.
137. **Tyynismaa H, Raivio T, Hakkarainen A, Ortega-Alonso A, Lundbom N, Kaprio J, Rissanen A, Suomalainen A, Pietiläinen KH.** Liver fat but not other adiposity measures influence circulating FGF21 levels in healthy young adult twins. *J. Clin. Endocrinol. Metab.* 2011;96(2):E351-355.
138. **Yilmaz Y, Eren F, Yonal O, Kurt R, Aktas B, Celikel CA, Ozdogan O, Imeryuz N, Kalayci C, Avsar E.** Increased serum FGF21 levels in patients with nonalcoholic fatty liver disease. *Eur. J. Clin. Invest.* 2010;40(10):887–892.
139. **Li X, Fan X, Ren F, Zhang Y, Shen C, Ren G, Sun J, Zhang N, Wang W, Ning G, Yang J.** Serum FGF21 levels are increased in newly diagnosed type 2 diabetes with nonalcoholic fatty liver disease and associated with hsCRP levels independently. *Diabetes Res. Clin. Pract.* 2011;93(1):10–16.
140. **Dasarathy S, Yang Y, McCullough AJ, Marczewski S, Bennett C, Kalhan SC.** Elevated hepatic fatty acid oxidation, high plasma fibroblast growth factor 21, and fasting bile acids in nonalcoholic steatohepatitis. *Eur. J. Gastroenterol. Hepatol.* 2011;23(5):382–388.
141. **Stefan N, Kantartzis K, Häring H-U.** Causes and metabolic consequences of Fatty liver. *Endocr. Rev.* 2008;29(7):939–960.
142. **Chavez AO, Molina-Carrion M, Abdul-Ghani MA, Folli F, Defronzo RA, Tripathy D.** Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. *Diabetes Care* 2009;32(8):1542–1546.
143. **Chen C, Cheung BMY, Tso AWK, Wang Y, Law LSC, Ong KL, Wat NMS, Xu A, Lam KSL.** High plasma level of fibroblast growth factor 21 is an Independent predictor of

type 2 diabetes: a 5.4-year population-based prospective study in Chinese subjects. *Diabetes Care* 2011;34(9):2113–2115.

144. **Lin Z, Gong Q, Wu C, Yu J, Lu T, Pan X, Lin S, Li X.** Dynamic change of serum FGF21 levels in response to glucose challenge in human. *J. Clin. Endocrinol. Metab.* 2012;97(7):E1224-1228.

145. **Chen W-W, Li L, Yang G-Y, Li K, Qi X-Y, Zhu W, Tang Y, Liu H, Boden G.** Circulating FGF-21 levels in normal subjects and in newly diagnose patients with Type 2 diabetes mellitus. *Exp. Clin. Endocrinol. Diabetes Off. J. Ger. Soc. Endocrinol. Ger. Diabetes Assoc.* 2008;116(1):65–68.

146. **Li L, Yang G, Ning H, Yang M, Liu H, Chen W.** Plasma FGF-21 levels in type 2 diabetic patients with ketosis. *Diabetes Res. Clin. Pract.* 2008;82(2):209–213.

147. **An S-Y, Lee MS, Yi S-A, Ha ES, Han SJ, Kim HJ, Kim DJ, Lee K-W.** Serum fibroblast growth factor 21 was elevated in subjects with type 2 diabetes mellitus and was associated with the presence of carotid artery plaques. *Diabetes Res. Clin. Pract.* 2012;96(2):196–203.

148. **Wang D, Zhu W, Li J, An C, Wang Z.** Serum concentrations of fibroblast growth factors 19 and 21 in women with gestational diabetes mellitus: association with insulin resistance, adiponectin, and polycystic ovary syndrome history. *PloS One* 2013;8(11):e81190.

149. **Li S, Wang W, Zhou L, Ma L, An Y, Xu W, Li T, Yu Y, Li D, Liu Y.** Fibroblast growth factor 21 expressions in white blood cells and sera of patients with gestational diabetes mellitus during gestation and postpartum. *Endocrine* 2015;48(2):519–527.

150. **Lin Y, Xiao Y, Zhu H, Xu Q, Qi L, Wang Y, Li X, Zheng M, Zhong R, Zhang Y, Xu X, Wu B, Xu Z, Lu X.** Serum fibroblast growth factor 21 levels are correlated with the severity of diabetic retinopathy. *J. Diabetes Res.* 2014;2014:929756.

151. **Esteghamati A, Momeni A, Abdollahi A, Khandan A, Afarideh M, Noshad S, Nakhjavani M.** Serum fibroblast growth factor 21 concentrations in type 2 diabetic retinopathy patients. *Ann. Endocrinol.* 2016;77(5):586–592.

152. **Stein S, Bachmann A, Lössner U, Kratzsch J, Blüher M, Stumvoll M, Fasshauer M.** Serum levels of the adipokine FGF21 depend on renal function. *Diabetes Care* 2009;32(1):126–128.

153. **Han SH, Choi SH, Cho BJ, Lee Y, Lim S, Park YJ, Moon MK, Lee HK, Kang S-W, Han DS, Kim Y-B, Jang HC, Park KS.** Serum fibroblast growth factor-21 concentration is associated with residual renal function and insulin resistance in end-stage renal disease patients receiving long-term peritoneal dialysis. *Metabolism.* 2010;59(11):1656–1662.

154. **Lin Z, Zhou Z, Liu Y, Gong Q, Yan X, Xiao J, Wang X, Lin S, Feng W, Li X.** Circulating FGF21 levels are progressively increased from the early to end stages of chronic kidney diseases and are associated with renal function in Chinese. *PloS One* 2011;6(4):e18398.

155. **Jian W-X, Peng W-H, Jin J, Chen X-R, Fang W-J, Wang W-X, Qin L, Dong Y, Su Q.** Association between serum fibroblast growth factor 21 and diabetic nephropathy. *Metabolism.* 2012;61(6):853–859.

156. Hindricks J, Ebert T, Bachmann A, Kralisch S, Lössner U, Kratzsch J, Stolzenburg J-U, Dietel A, Beige J, Anders M, Bast I, Blüher M, Stumvoll M, Fasshauer M. Serum levels of fibroblast growth factor-21 are increased in chronic and acute renal dysfunction. *Clin. Endocrinol. (Oxf.)* 2014;80(6):918–924.

157. **Lee CH, Hui EYL, Woo YC, Yeung CY, Chow WS, Yuen MMA, Fong CHY, Xu A, Lam KSL.** Circulating fibroblast growth factor 21 levels predict progressive kidney disease in subjects with type 2 diabetes and normoalbuminuria. *J. Clin. Endocrinol. Metab.* 2015;100(4):1368–1375.

158. **Lin Z, Wu Z, Yin X, Liu Y, Yan X, Lin S, Xiao J, Wang X, Feng W, Li X.** Serum levels of FGF-21 are increased in coronary heart disease patients and are independently associated with adverse lipid profile. *PloS One* 2010;5(12):e15534.
159. **Stein S, Stepan H, Kratzsch J, Verlohren M, Verlohren H-J, Drynda K, Lössner U, Blüher M, Stumvoll M, Fasshauer M.** Serum fibroblast growth factor 21 levels in gestational diabetes mellitus in relation to insulin resistance and dyslipidemia. *Metabolism.* 2010;59(1):33–37.
160. **Kralisch S, Tönjes A, Krause K, Richter J, Lossner U, Kovacs P, Ebert T, Blüher M, Stumvoll M, Fasshauer M.** Fibroblast growth factor-21 serum concentrations are associated with metabolic and hepatic markers in humans. *J. Endocrinol.* 2013;216(2):135–143.
161. **Shen Y, Ma X, Zhou J, Pan X, Hao Y, Zhou M, Lu Z, Gao M, Bao Y, Jia W.** Additive relationship between serum fibroblast growth factor 21 level and coronary artery disease. *Cardiovasc. Diabetol.* 2013;12:124.
162. **Jin Q-R, Bando Y, Miyawaki K, Shikama Y, Kosugi C, Aki N, Funaki M, Noji S.** Correlation of fibroblast growth factor 21 serum levels with metabolic parameters in Japanese subjects. *J. Med. Investig. JMI* 2014;61(1–2):28–34.
163. **Chow WS, Xu A, Woo YC, Tso AWK, Cheung SCW, Fong CHY, Tse HF, Chau MT, Cheung BMY, Lam KSL.** Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors. *Arterioscler. Thromb. Vasc. Biol.* 2013;33(10):2454–2459.
164. **Ulu SM, Yuksel S, Altuntaş A, Kacar E, Ahsen A, Altug A, Celik S, Sezer MT.** Associations between serum hepcidin level, FGF-21 level and oxidative stress with arterial stiffness in CAPD patients. *Int. Urol. Nephrol.* 2014;46(12):2409–2414.
165. **Zhang X, Hu Y, Zeng H, Li L, Zhao J, Zhao J, Liu F, Bao Y, Jia W.** Serum fibroblast growth factor 21 levels is associated with lower extremity atherosclerotic disease in Chinese female diabetic patients. *Cardiovasc. Diabetol.* 2015;14:32.
166. **Xiao Y, Liu L, Xu A, Zhou P, Long Z, Tu Y, Chen X, Tang W, Huang G, Zhou Z.** Serum fibroblast growth factor 21 levels are related to subclinical atherosclerosis in patients with type 2 diabetes. *Cardiovasc. Diabetol.* 2015;14:72.
167. **Yang SJ, Hong HC, Choi HY, Yoo HJ, Cho GJ, Hwang TG, Baik SH, Choi DS, Kim SM, Choi KM.** Effects of a three-month combined exercise programme on fibroblast growth factor 21 and fetuin-A levels and arterial stiffness in obese women. *Clin. Endocrinol. (Oxf.)* 2011;75(4):464–469.
168. **Kim WJ, Kim SS, Lee HC, Song SH, Bae MJ, Yi YS, Jeon YK, Kim BH, Kim YK, Kim IJ.** Association between Serum Fibroblast Growth Factor 21 and Coronary Artery Disease in Patients with Type 2 Diabetes. *J. Korean Med. Sci.* 2015;30(5):586–590.
169. **Zhang W, Chu S, Ding W, Wang F.** Serum Level of Fibroblast Growth Factor 21 Is Independently Associated with Acute Myocardial Infarction. *PloS One* 2015;10(6):e0129791.
170. **Semba RD, Crasto C, Strait J, Sun K, Schaumberg DA, Ferrucci L.** Elevated serum fibroblast growth factor 21 is associated with hypertension in community-dwelling adults. *J. Hum. Hypertens.* 2013;27(6):397–399.
171. Stepan H, Kley K, Hindricks J, Kralisch S, Jank A, Schaarschmidt W, Schrey S, Ebert T, Lössner U, Kratzsch J, Blüher M, Stumvoll M, Richter J, Fasshauer M. Serum levels of the adipokine fibroblast growth factor-21 are increased in preeclampsia. *Cytokine* 2013;62(2):322–326.
172. Wei W, Dutchak PA, Wang X, Ding X, Wang X, Bookout AL, Goetz R, Mohammadi M, Gerard RD, Dechow PC, Mangelsdorf DJ, Kliewer SA, Wan Y. Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor γ. *Proc. Natl. Acad. Sci. U. S. A.* 2012;109(8):3143–3148.

173. **Hanks LJ, Casazza K, Ashraf AP, Wallace S, Gutiérrez OM.** Fibroblast growth factor-21, body composition, and insulin resistance in pre-pubertal and early pubertal males and females. *Clin. Endocrinol. (Oxf.)* 2015;82(4):550–556.
174. **Fazeli PK, Faje AT, Cross EJ, Lee H, Rosen CJ, Bouxsein ML, Klibanski A.** Serum FGF-21 levels are associated with worsened radial trabecular bone microarchitecture and decreased radial bone strength in women with anorexia nervosa. *Bone* 2015;77:6–11.
175. **Li Z-C, Xiao J, Wang G, Li M-Q, Hu K-Z, Ma T, Wang W-L, Liu Z-D, Zhang J-D.** Fibroblast growth factor-21 concentration in serum and synovial fluid is associated with radiographic bone loss of knee osteoarthritis. *Scand. J. Clin. Lab. Invest.* 2015;75(2):121–125.
176. Tyynismaa H, Carroll CJ, Raimundo N, Ahola-Erkkilä S, Wenz T, Ruhanen H, Guse K, Hemminki A, Peltola-Mjøsund KE, Tulkki V, Oresic M, Moraes CT, Pietiläinen K, Hovatta I, Suomalainen A. Mitochondrial myopathy induces a starvation-like response. *Hum. Mol. Genet.* 2010;19(20):3948–3958.
177. Kim KH, Jeong YT, Oh H, Kim SH, Cho JM, Kim Y-N, Kim SS, Kim DH, Hur KY, Kim HK, Ko T, Han J, Kim HL, Kim J, Back SH, Komatsu M, Chen H, Chan DC, Konishi M, Itoh N, Choi CS, Lee M-S. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. *Nat. Med.* 2013;19(1):83–92.
178. Brahma MK, Adam RC, Pollak NM, Jaeger D, Zierler KA, Pöcher N, Schreiber R, Romauch M, Moustafa T, Eder S, Ruelicke T, Preiss-Landl K, Lass A, Zechner R, Haemmerle G. Fibroblast growth factor 21 is induced upon cardiac stress and alters cardiac lipid homeostasis. *J. Lipid Res.* 2014;55(11):2229–2241.
179. **Keipert S, Ost M, Johann K, Imber F, Jastroch M, van Schothorst EM, Keijer J, Klaus S.** Skeletal muscle mitochondrial uncoupling drives endocrine cross-talk through the induction of FGF21 as a myokine. *AJP Endocrinol. Metab.* 2014;306(5):E469–E482.
180. **Harris L-ALS, Skinner JR, Shew TM, Pietka TA, Abumrad NA, Wolins NE.** Perilipin 5-Driven Lipid Droplet Accumulation in Skeletal Muscle Stimulates the Expression of Fibroblast Growth Factor 21. *Diabetes* 2015;64(8):2757–2768.
181. **Crooks DR, Natarajan TG, Jeong SY, Chen C, Park SY, Huang H, Ghosh MC, Tong W-H, Haller RG, Wu C, Rouault TA.** Elevated FGF21 secretion, PGC-1α and ketogenic enzyme expression are hallmarks of iron-sulfur cluster depletion in human skeletal muscle. *Hum. Mol. Genet.* 2014;23(1):24–39.
182. **Magner M, Kolářová H, Honzik T, Švandová I, Zeman J.** Clinical manifestation of mitochondrial diseases. *Dev. Period Med.* 2015;19(4):441–449.
183. Suomalainen A, Elo JM, Pietiläinen KH, Hakonen AH, Sevastianova K, Korpela M, Isohanni P, Marjavaara SK, Tyni T, Kiuru-Enari S, Pihko H, Darin N, Õunap K, Kluijtmans LAJ, Paetau A, Buzkova J, Bindoff LA, Annunen-Rasila J, Uusimaa J, Rissanen A, Yki-Järvinen H, Hirano M, Tulinius M, Smeitink J, Tyynismaa H. FGF-21 as a biomarker for muscle-manifesting mitochondrial respiratory chain deficiencies: a diagnostic study. *Lancet Neurol.* 2011;10(9):806–818.
184. Su S-L, Wang W-F, Wu S-L, Wu H-M, Chang J-C, Huang C-S, Cheng W-L, Soong B-W, Lee Y-C, Li J-Y, Kuo S-J, Chen M, Huang C-N, Liu C-S. FGF21 in ataxia patients with spinocerebellar atrophy and mitochondrial disease. *Clin. Chim. Acta Int. J. Clin. Chem.* 2012;414:225–227.
185. **Salehi MH, Kamalidehghan B, Houshmand M, Aryani O, Sadeghizadeh M, Mossalaeie MM.** Association of fibroblast growth factor (FGF-21) as a biomarker with primary mitochondrial disorders, but not with secondary mitochondrial disorders (Friedreich Ataxia). *Mol. Biol. Rep.* 2013;40(11):6495–6499.

186. **Davis RL, Liang C, Edema-Hildebrand F, Riley C, Needham M, Sue CM.** Fibroblast growth factor 21 is a sensitive biomarker of mitochondrial disease. *Neurology* 2013;81(21):1819–1826.
187. **Ji K, Zheng J, Lv J, Xu J, Ji X, Luo Y-B, Li W, Zhao Y, Yan C.** Skeletal muscle increases FGF21 expression in mitochondrial disorders to compensate for energy metabolic insufficiency by activating the mTOR-YY1-PGC1α pathway. *Free Radic. Biol. Med.* 2015;84:161–170.
188. Vandanmagsar B, Warfel JD, Wicks SE, Ghosh S, Salbaum JM, Burk D, Dubuisson OS, Mendoza TM, Zhang J, Noland RC, Mynatt RL. Impaired mitochondrial fat oxidation induces FGF21 in muscle. *Cell Rep.* 2016;15(8):1686–1699.
189. **Montgomery MK, Turner N.** Mitochondrial dysfunction and insulin resistance: an update. *Endocr. Connect.* 2015;4(1):R1–R15.
190. **Paradies G, Paradies V, Ruggiero FM, Petrosillo G.** Oxidative stress, cardiolipin and mitochondrial dysfunction in nonalcoholic fatty liver disease. *World J. Gastroenterol.* 2014;20(39):14205–14218.
191. **Supale S, Li N, Brun T, Maechler P.** Mitochondrial dysfunction in pancreatic β cells. *Trends Endocrinol. Metab. TEM* 2012;23(9):477–487.
192. **Omar BA, Andersen B, Hald J, Raun K, Nishimura E, Ahrén B.** Fibroblast growth factor 21 (FGF21) and glucagon-like peptide 1 contribute to diabetes resistance in glucagon receptor-deficient mice. *Diabetes* 2014;63(1):101–110.
193. **Johnson CL, Mehmood R, Laing SW, Stepniak CV, Kharitonenkov A, Pin CL.** Silencing of the Fibroblast growth factor 21 gene is an underlying cause of acinar cell injury in mice lacking MIST1. *Am. J. Physiol. Endocrinol. Metab.* 2014;306(8):E916-928.
194. **Johnson CL, Weston JY, Chadi SA, Fazio EN, Huff MW, Kharitonenkov A, Köester A, Pin CL.** Fibroblast growth factor 21 reduces the severity of cerulein-induced pancreatitis in mice. *Gastroenterology* 2009;137(5):1795–1804.
195. **Shenoy VK, Beaver KM, Fisher ffolliott M, Singhal G, Dushay JR, Maratos-Flier E, Flier SN.** Elevated Serum Fibroblast Growth Factor 21 in Humans with Acute Pancreatitis. *PLOS ONE* 2016;11(11):e0164351.
196. **Domingo P, Gallego-Escuredo JM, Domingo JC, Gutiérrez M del M, Mateo MG, Fernández I, Vidal F, Giralt M, Villarroya F.** Serum FGF21 levels are elevated in association with lipodystrophy, insulin resistance and biomarkers of liver injury in HIV-1-infected patients. *AIDS Lond. Engl.* 2010;24(17):2629–2637.
197. **Miehle K, Ebert T, Kralisch S, Hoffmann A, Kratzsch J, Schlögl H, Stumvoll M, Fasshauer M.** Serum concentrations of fibroblast growth factor 21 are elevated in patients with congenital or acquired lipodystrophy. *Cytokine* 2016;83:239–244.
198. **Ge X, Chen C, Hui X, Wang Y, Lam KSL, Xu A.** Fibroblast growth factor 21 induces glucose transporter-1 expression through activation of the serum response factor/Ets-like protein-1 in adipocytes. *J. Biol. Chem.* 2011;286(40):34533–34541.
199. **Gallego-Escuredo JM, Gómez-Ambrosi J, Catalan V, Domingo P, Giralt M, Frühbeck G, Villarroya F.** Opposite alterations in FGF21 and FGF19 levels and disturbed expression of the receptor machinery for endocrine FGFs in obese patients. *Int. J. Obes. 2005* 2015;39(1):121–129.
200. **Markan KR, Naber MC, Small SM, Peltekian L, Kessler RL, Potthoff MJ.** FGF21 resistance is not mediated by downregulation of beta-klotho expression in white adipose tissue. *Mol. Metab.* 2017. doi:10.1016/j.molmet.2017.03.009.
201. **Adams AC, Coskun T, Cheng CC, O Farrell LS, Dubois SL, Kharitonenkov A.** Fibroblast growth factor 21 is not required for the antidiabetic actions of the thiazoladinediones. *Mol. Metab.* 2013;2(3):205–214.

202. **Yang W, Chen X, Liu Y, Chen M, Jiang X, Shen T, Li Q, Yang Y, Ling W.** N-3 polyunsaturated fatty acids increase hepatic fibroblast growth factor 21 sensitivity via a PPARγ-β-klotho pathway. *Mol. Nutr. Food Res.* 2017. doi:10.1002/mnfr.201601075.
203. **Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, Chen Y, Moller DE, Kharitonenkov A.** Fibroblast growth factor 21 corrects obesity in mice. *Endocrinology* 2008;149(12):6018–6027.
204. **Berglund ED, Li CY, Bina HA, Lynes SE, Michael MD, Shanafelt AB, Kharitonenkov A, Wasserman DH.** Fibroblast growth factor 21 controls glycemia via regulation of hepatic glucose flux and insulin sensitivity. *Endocrinology* 2009;150(9):4084–4093.
205. **Gaich G, Chien JY, Fu H, Glass LC, Deeg MA, Holland WL, Kharitonenkov A, Bumol T, Schilske HK, Moller DE.** The Effects of LY2405319, an FGF21 Analog, in Obese Human Subjects with Type 2 Diabetes. *Cell Metab.* 2013;18(3):333–340.
206. **Dong JQ, Rossulek M, Somayaji VR, Baltrukonis D, Liang Y, Hudson K, Hernandez-Illas M, Calle RA.** Pharmacokinetics and pharmacodynamics of PF-05231023, a novel long-acting FGF21 mimetic, in a first-in-human study. *Br. J. Clin. Pharmacol.* 2015;80(5):1051–1063.
207. Talukdar S, Zhou Y, Li D, Rossulek M, Dong J, Somayaji V, Weng Y, Clark R, Lanba A, Owen BM, Brenner MB, Trimmer JK, Gropp KE, Chabot JR, Erion DM, Rolph TP, Goodwin B, Calle RA. A Long-Acting FGF21 Molecule, PF-05231023, Decreases Body Weight and Improves Lipid Profile in Non-human Primates and Type 2 Diabetic Subjects. *Cell Metab.* 2016;23(3):427–440.
208. **Kim AM, Somayaji VR, Dong JQ, Rolph TP, Weng Y, Chabot JR, Gropp KE, Talukdar S, Calle RA.** Once-weekly administration of a long-acting FGF21 analogue modulates lipids, bone turnover markers, blood pressure, and body weight differently in obese hypertriglyceridemic subjects and in non-human primates. *Diabetes Obes. Metab.*:n/a-n/a.
209. Kharitonenkov A, Beals JM, Micanovic R, Strifler BA, Rathnachalam R, Wroblewski VJ, Li S, Koester A, Ford AM, Coskun T, Dunbar JD, Cheng CC, Frye CC, Bumol TF, Moller DE. Rational design of a fibroblast growth factor 21-based clinical candidate, LY2405319. *PloS One* 2013;8(3):e58575.
210. **Zhang J, Li Y.** Fibroblast Growth Factor 21 Analogs for Treating Metabolic Disorders. *Front. Endocrinol.* 2015;6:168.
211. **Degirolamo C, Sabbà C, Moschetta A.** Therapeutic potential of the endocrine fibroblast growth factors FGF19, FGF21 and FGF23. *Nat. Rev. Drug Discov.* 2016;15(1):51–69.
212. **Inagaki T, Lin VY, Goetz R, Mohammadi M, Mangelsdorf DJ, Kliewer SA.** Inhibition of growth hormone signaling by the fasting-induced hormone FGF21. *Cell Metab.* 2008;8(1):77–83.
213. Zhang Y, Xie Y, Berglund ED, Coate KC, He TT, Katafuchi T, Xiao G, Potthoff MJ, Wei W, Wan Y, Yu RT, Evans RM, Kliewer SA, Mangelsdorf DJ. The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. *eLife* 2012;1:e00065.
214. **Mericq V, De Luca F, Hernandez MI, Peña V, Rossel K, Garcia M, Avila A, Cavada G, Iñiguez G.** Serum fibroblast growth factor 21 levels are inversely associated with growth rates in infancy. *Horm. Res. Paediatr.* 2014;82(5):324–331.
215. **Adams AC, Yang C, Coskun T, Cheng CC, Gimeno RE, Luo Y, Kharitonenkov A.** The breadth of FGF21's metabolic actions are governed by FGFR1 in adipose tissue. *Mol. Metab.* 2012;2(1):31–37.
216. Foltz IN, Hu S, King C, Wu X, Yang C, Wang W, Weiszmann J, Stevens J, Chen JS, Nuanmanee N, Gupte J, Komorowski R, Sekirov L, Hager T, Arora T, Ge H, Baribault H,

Wang F, Sheng J, Karow M, Wang M, Luo Y, McKeehan W, Wang Z, Véniant MM, Li Y. Treating diabetes and obesity with an FGF21-mimetic antibody activating the βKlotho/FGFR1c receptor complex. *Sci. Transl. Med.* 2012;4(162):162ra153.
217. **Véniant MM, Hale C, Helmering J, Chen MM, Stanislaus S, Busby J, Vonderfecht S, Xu J, Lloyd DJ.** FGF21 promotes metabolic homeostasis via white adipose and leptin in mice. *PloS One* 2012;7(7):e40164.
218. **Arner P, Pettersson A, Mitchell PJ, Dunbar JD, Kharitonenkov A, Rydén M.** FGF21 attenuates lipolysis in human adipocytes - a possible link to improved insulin sensitivity. *FEBS Lett.* 2008;582(12):1725–1730.
219. **Li K, Li L, Yang M, Liu H, Boden G, Yang G.** The effects of fibroblast growth factor-21 knockdown and over-expression on its signaling pathway and glucose-lipid metabolism in vitro. *Mol. Cell. Endocrinol.* 2012;348(1):21–26.
220. **Li X, Ge H, Weiszmann J, Hecht R, Li Y, Véniant MM, Xu J, Wu X, Lindberg R, Li Y.** Inhibition of lipolysis may contribute to the acute regulation of plasma FFA and glucose by FGF21 in ob/ob mice. *FEBS Lett.* 2009;583(19):3230–3234.
221. **Hotta Y, Nakamura H, Konishi M, Murata Y, Takagi H, Matsumura S, Inoue K, Fushiki T, Itoh N.** Fibroblast growth factor 21 regulates lipolysis in white adipose tissue but is not required for ketogenesis and triglyceride clearance in liver. *Endocrinology* 2009;150(10):4625–4633.
222. **Liu L, Zhao C, Yang Y, Kong X, Shao T, Ren L, Zhuang X, Yin B, Dryden G, McClain C, Luan W, Feng W.** Fibroblast Growth Factor 21 Deficiency Attenuates Experimental Colitis-Induced Adipose Tissue Lipolysis. *Gastroenterol. Res. Pract.* 2017;2017:e3089378.
223. **Wang ZV, Scherer PE.** Adiponectin, the past two decades. *J. Mol. Cell Biol.* 2016;8(2):93–100.
224. **Ye R, Scherer PE.** Adiponectin, driver or passenger on the road to insulin sensitivity? *Mol. Metab.* 2013;2(3):133–141.
225. **Lin Z, Tian H, Lam KSL, Lin S, Hoo RCL, Konishi M, Itoh N, Wang Y, Bornstein SR, Xu A, Li X.** Adiponectin Mediates the Metabolic Effects of FGF21 on Glucose Homeostasis and Insulin Sensitivity in Mice. *Cell Metab.* 2013;17(5):779–789.
226. Holland WL, Adams AC, Brozinick JT, Bui HH, Miyauchi Y, Kusminski CM, Bauer SM, Wade M, Singhal E, Cheng CC, Volk K, Kuo M-S, Gordillo R, Kharitonenkov A, Scherer PE. An FGF21-adiponectin-ceramide axis controls energy expenditure and insulin action in mice. *Cell Metab.* 2013;17(5):790–797.
227. Bernardo B, Lu M, Bandyopadhyay G, Li P, Zhou Y, Huang J, Levin N, Tomas EM, Calle RA, Erion DM, Rolph TP, Brenner M, Talukdar S. FGF21 does not require interscapular brown adipose tissue and improves liver metabolic profile in animal models of obesity and insulin-resistance. *Sci. Rep.* 2015;5:11382.
228. Mottillo EP, Desjardins EM, Fritzen AM, Zou VZ, Crane JD, Yabut JM, Kiens B, Erion DM, Lanba A, Granneman JG, Talukdar S, Steinberg GR. FGF21 does not require adipocyte AMP-activated protein kinase (AMPK) or the phosphorylation of acetyl-CoA carboxylase (ACC) to mediate improvements in whole-body glucose homeostasis. *Mol. Metab.* 2017;6(6):471–481.
229. **Schlein C, Talukdar S, Heine M, Fischer AW, Krott LM, Nilsson SK, Brenner MB, Heeren J, Scheja L.** FGF21 Lowers Plasma Triglycerides by Accelerating Lipoprotein Catabolism in White and Brown Adipose Tissues. *Cell Metab.* 2016;23(3):441–453.
230. Wu J, Boström P, Sparks LM, Ye L, Choi JH, Giang A-H, Khandekar M, Virtanen KA, Nuutila P, Schaart G, Huang K, Tu H, van Marken Lichtenbelt WD, Hoeks J, Enerbäck S, Schrauwen P, Spiegelman BM. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* 2012;150(2):366–376.

231. **Gao M, Ma Y, Cui R, Liu D.** Hydrodynamic delivery of FGF21 gene alleviates obesity and fatty liver in mice fed a high-fat diet. *J. Control. Release Off. J. Control. Release Soc.* 2014;185:1–11.
232. **Owen BM, Ding X, Morgan DA, Coate KC, Bookout AL, Rahmouni K, Kliewer SA, Mangelsdorf DJ.** FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. *Cell Metab.* 2014;20(4):670–677.
233. Douris N, Stevanovic DM, Fisher ffolliott M, Cisu TI, Chee MJ, Nguyen NL, Zarebidaki E, Adams AC, Kharitonenkov A, Flier JS, Bartness TJ, Maratos-Flier E. Central Fibroblast Growth Factor 21 Browns White Fat via Sympathetic Action in Male Mice. *Endocrinology* 2015;156(7):2470–2481.
234. **Véniant MM, Sivits G, Helmering J, Komorowski R, Lee J, Fan W, Moyer C, Lloyd DJ.** Pharmacologic Effects of FGF21 Are Independent of the "Browning" of White Adipose Tissue. *Cell Metab.* 2015;21(5):731–738.
235. **Samms RJ, Smith DP, Cheng CC, Antonellis PP, Perfield JW, Kharitonenkov A, Gimeno RE, Adams AC.** Discrete Aspects of FGF21 In Vivo Pharmacology Do Not Require UCP1. *Cell Rep.* 2015;11(7):991–999.
236. Hanssen MJW, Broeders E, Samms RJ, Vosselman MJ, van der Lans AAJJ, Cheng CC, Adams AC, van Marken Lichtenbelt WD, Schrauwen P. Serum FGF21 levels are associated with brown adipose tissue activity in humans. *Sci. Rep.* 2015;5:10275.
237. Xu J, Lloyd DJ, Hale C, Stanislaus S, Chen M, Sivits G, Vonderfecht S, Hecht R, Li Y-S, Lindberg RA, Chen J-L, Jung DY, Zhang Z, Ko H-J, Kim JK, Véniant MM. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. *Diabetes* 2009;58(1):250–259.
238. **Zhang Y, Lei T, Huang JF, Wang SB, Zhou LL, Yang ZQ, Chen XD.** The link between fibroblast growth factor 21 and sterol regulatory element binding protein 1c during lipogenesis in hepatocytes. *Mol. Cell. Endocrinol.* 2011;342(1–2):41–47.
239. **Camporez JPG, Jornayvaz FR, Petersen MC, Pesta D, Guigni BA, Serr J, Zhang D, Kahn M, Samuel VT, Jurczak MJ, Shulman GI.** Cellular mechanisms by which FGF21 improves insulin sensitivity in male mice. *Endocrinology* 2013;154(9):3099–3109.
240. **Camporez JPG, Asrih M, Zhang D, Kahn M, Samuel VT, Jurczak MJ, Jornayvaz FR.** Hepatic insulin resistance and increased hepatic glucose production in mice lacking Fgf21. *J. Endocrinol.* 2015;226(3):207–217.
241. **Potthoff MJ, Inagaki T, Satapati S, Ding X, He T, Goetz R, Mohammadi M, Finck BN, Mangelsdorf DJ, Kliewer SA, Burgess SC.** FGF21 induces PGC-1alpha and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response. *Proc. Natl. Acad. Sci. U. S. A.* 2009;106(26):10853–10858.
242. **Zhang J, Gupte J, Gong Y, Weiszmann J, Zhang Y, Lee KJ, Richards WG, Li Y.** Chronic Over-expression of Fibroblast Growth Factor 21 Increases Bile Acid Biosynthesis by Opposing FGF15/19 Action. *EBioMedicine* 2017;15:173–183.
243. **Woolsey SJ, Beaton MD, Mansell SE, Leon-Ponte M, Yu J, Pin CL, Adams PC, Kim RB, Tirona RG.** A Fibroblast Growth Factor 21-Pregnane X Receptor Pathway Downregulates Hepatic CYP3A4 in Nonalcoholic Fatty Liver Disease. *Mol. Pharmacol.* 2016;90(4):437–446.
244. **Wente W, Efanov AM, Brenner M, Kharitonenkov A, Köster A, Sandusky GE, Sewing S, Treinies I, Zitzer H, Gromada J.** Fibroblast growth factor-21 improves pancreatic beta-cell function and survival by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways. *Diabetes* 2006;55(9):2470–2478.
245. **So WY, Cheng Q, Xu A, Lam KSL, Leung PS.** Loss of fibroblast growth factor 21 action induces insulin resistance, pancreatic islet hyperplasia and dysfunction in mice. *Cell Death Dis.* 2015;6:e1707.

246. **So WY, Cheng Q, Chen L, Evans-Molina C, Xu A, Lam KSL, Leung PS.** High glucose represses β-klotho expression and impairs fibroblast growth factor 21 action in mouse pancreatic islets: involvement of peroxisome proliferator-activated receptor γ signaling. *Diabetes* 2013;62(11):3751–3759.
247. **Mäkelä J, Tselykh TV, Maiorana F, Eriksson O, Do HT, Mudò G, Korhonen LT, Belluardo N, Lindholm D.** Fibroblast growth factor-21 enhances mitochondrial functions and increases the activity of PGC-1α in human dopaminergic neurons via Sirtuin-1. *SpringerPlus* 2014;3:2.
248. **Huang X, Hu J, Li Y, Zhuyun Yang Z, Zhu H, Zhou L, Ma K, Schachner M, Xiao Z, Li Y.** The cell adhesion molecule L1 regulates the expression of FGF21 and enhances neurite outgrowth. *Brain Res.* 2013;1530:13–21.
249. **Hsuchou H, Pan W, Kastin AJ.** The fasting polypeptide FGF21 can enter brain from blood. *Peptides* 2007;28(12):2382–2386.
250. **Tan BK, Hallschmid M, Adya R, Kern W, Lehnert H, Randeva HS.** Fibroblast Growth Factor 21 (FGF21) in Human Cerebrospinal Fluid. *Diabetes* 2011;60(11):2758–2762.
251. Bookout AL, de Groot MHM, Owen BM, Lee S, Gautron L, Lawrence HL, Ding X, Elmquist JK, Takahashi JS, Mangelsdorf DJ, Kliewer SA. FGF21 regulates metabolism and circadian behavior by acting on the nervous system. *Nat. Med.* 2013;19(9):1147–1152.
252. **Liang Q, Zhong L, Zhang J, Wang Y, Bornstein SR, Triggle CR, Ding H, Lam KSL, Xu A.** FGF21 maintains glucose homeostasis by mediating the cross talk between liver and brain during prolonged fasting. *Diabetes* 2014;63(12):4064–4075.
253. Bornstein S, Brown SA, Le PT, Wang X, DeMambro V, Horowitz MC, MacDougald O, Baron R, Lotinun S, Karsenty G, Wei W, Ferron M, Kovacs CS, Clemmons D, Wan Y, Rosen CJ. FGF-21 and skeletal remodeling during and after lactation in C57BL/6J mice. *Endocrinology* 2014;155(9):3516–3526.
254. **Wang X, Wei W, Krzeszinski JY, Wang Y, Wan Y.** A Liver-Bone Endocrine Relay by IGFBP1 Promotes Osteoclastogenesis and Mediates FGF21-Induced Bone Resorption. *Cell Metab.* 2015;22(5):811–824.
255. Kaess BM, Barnes TA, Stark K, Charchar FJ, Waterworth D, Song K, Wang WYS, Vollenweider P, Waeber G, Mooser V, Zukowska-Szczechowska E, Samani NJ, Hengstenberg C, Tomaszewski M. FGF21 signalling pathway and metabolic traits – genetic association analysis. *Eur. J. Hum. Genet.* 2010;18(12):1344–1348.
256. Chu AY, Workalemahu T, Paynter NP, Rose LM, Giulianini F, Tanaka T, Ngwa JS, CHARGE Nutrition Working Group, Qi Q, Curhan GC, Rimm EB, Hunter DJ, Pasquale LR, Ridker PM, Hu FB, Chasman DI, Qi L, DietGen Consortium. Novel locus including FGF21 is associated with dietary macronutrient intake. *Hum. Mol. Genet.* 2013;22(9):1895–1902.
257. Tanaka T, Ngwa JS, van Rooij FJA, Zillikens MC, Wojczynski MK, Frazier-Wood AC, Houston DK, Kanoni S, Lemaitre RN, Luan J, Mikkilä V, Renstrom F, Sonestedt E, Zhao JH, Chu AY, Qi L, Chasman DI, de Oliveira Otto MC, Dhurandhar EJ, Feitosa MF, Johansson I, Khaw K-T, Lohman KK, Manichaikul A, McKeown NM, Mozaffarian D, Singleton A, Stirrups K, Viikari J, Ye Z, Bandinelli S, Barroso I, Deloukas P, Forouhi NG, Hofman A, Liu Y, Lyytikäinen L-P, North KE, Dimitriou M, Hallmans G, Kähönen M, Langenberg C, Ordovas JM, Uitterlinden AG, Hu FB, Kalafati I-P, Raitakari O, Franco OH, Johnson A, Emilsson V, Schrack JA, Semba RD, Siscovick DS, Arnett DK, Borecki IB, Franks PW, Kritchevsky SB, Lehtimäki T, Loos RJF, Orho-Melander M, Rotter JI, Wareham NJ, Witteman JCM, Ferrucci L, Dedoussis G, Cupples LA, Nettleton JA. Genome-wide meta-analysis of observational studies shows common genetic variants associated with macronutrient intake. *Am. J. Clin. Nutr.* 2013;97(6):1395–1402.
258. Schumann G, Liu C, O'Reilly P, Gao H, Song P, Xu B, Ruggeri B, Amin N, Jia T, Preis S, Lepe MS, Akira S, Barbieri C, Baumeister S, Cauchi S, Clarke T-K, Enroth S,

Fischer K, Hällfors J, Harris SE, Hieber S, Hofer E, Hottenga J-J, Johansson Å, Joshi PK, Kaartinen N, Laitinen J, Lemaitre R, Loukola A, Luan J, Lyytikäinen L-P, Mangino M, Manichaikul A, Mbarek H, Milaneschi Y, Moayyeri A, Mukamal K, Nelson C, Nettleton J, Partinen E, Rawal R, Robino A, Rose L, Sala C, Satoh T, Schmidt R, Schraut K, Scott R, Smith AV, Starr JM, Teumer A, Trompet S, Uitterlinden AG, Venturini C, Vergnaud A-C, Verweij N, Vitart V, Vuckovic D, Wedenoja J, Yengo L, Yu B, Zhang W, Zhao JH, Boomsma DI, Chambers J, Chasman DI, Daniela T, Geus E de, Deary I, Eriksson JG, Esko T, Eulenburg V, Franco OH, Froguel P, Gieger C, Grabe HJ, Gudnason V, Gyllensten U, Harris TB, Hartikainen A-L, Heath AC, Hocking L, Hofman A, Huth C, Jarvelin M-R, Jukema JW, Kaprio J, Kooner JS, Kutalik Z, Lahti J, Langenberg C, Lehtimäki T, Liu Y, Madden PAF, Martin N, Morrison A, Penninx B, Pirastu N, Psaty B, Raitakari O, Ridker P, Rose R, Rotter JI, Samani NJ, Schmidt H, Spector TD, Stott D, Strachan D, Tzoulaki I, Harst P van der, Duijn CM van, Marques-Vidal P, Vollenweider P, Wareham NJ, Whitfield JB, Wilson J, Wolffenbuttel B, Bakalkin G, Evangelou E, Liu Y, Rice KM, Desrivières S, Kliewer SA, Mangelsdorf DJ, Müller CP, Levy D, Elliott P. KLB is associated with alcohol drinking, and its gene product β-Klotho is necessary for FGF21 regulation of alcohol preference. *Proc. Natl. Acad. Sci.* 2016;113(50):14372–14377.

259. **Guyard-Dangremont V, Desrumaux C, Gambert P, Lallemant C, Lagrost L.** Phospholipid and cholesteryl ester transfer activities in plasma from 14 vertebrate species. Relation to atherogenesis susceptibility. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* 1998;120(3):517–525.

260. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, McDonald-Smith GP, Gao H, Hennessy L, Finnerty CC, López CM, Honari S, Moore EE, Minei JP, Cuschieri J, Bankey PE, Johnson JL, Sperry J, Nathens AB, Billiar TR, West MA, Jeschke MG, Klein MB, Gamelli RL, Gibran NS, Brownstein BH, Miller-Graziano C, Calvano SE, Mason PH, Cobb JP, Rahme LG, Lowry SF, Maier RV, Moldawer LL, Herndon DN, Davis RW, Xiao W, Tompkins RG, Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc. Natl. Acad. Sci. U. S. A.* 2013;110(9):3507–3512.

261. **Tian XY, Ganeshan K, Hong C, Nguyen KD, Qiu Y, Kim J, Tangirala RK, Tontonoz P, Tonotonoz P, Chawla A.** Thermoneutral Housing Accelerates Metabolic Inflammation to Potentiate Atherosclerosis but Not Insulin Resistance. *Cell Metab.* 2016;23(1):165–178.

262. **BonDurant LD, Ameka M, Naber MC, Markan KR, Idiga SO, Acevedo MR, Walsh SA, Ornitz DM, Potthoff MJ.** FGF21 Regulates Metabolism Through Adipose-Dependent and -Independent Mechanisms. *Cell Metab.* 2017;25(4):935–944.e4.

263. **Kwon MM, O'Dwyer SM, Baker RK, Covey SD, Kieffer TJ.** FGF21-Mediated Improvements in Glucose Clearance Require Uncoupling Protein 1. *Cell Rep.* 2015;13(8):1521–1527.

264. Lehtonen JM, Forsström S, Bottani E, Viscomi C, Baris OR, Isoniemi H, Höckerstedt K, Österlund P, Hurme M, Jylhävä J, Leppä S, Markkula R, Heliö T, Mombelli G, Uusimaa J, Laaksonen R, Laaksovirta H, Auranen M, Zeviani M, Smeitink J, Wiesner RJ, Nakada K, Isohanni P, Suomalainen A. FGF21 is a biomarker for mitochondrial translation and mtDNA maintenance disorders. *Neurology* 2016;87(22):2290–2299.

265. **Kokkinos J, Tang S, Rye K-A, Ong KL.** The role of fibroblast growth factor 21 in atherosclerosis. *Atherosclerosis* 2017;257:259–265.

266. **Heni M, Kullmann S, Preissl H, Fritsche A, Häring H-U.** Impaired insulin action in the human brain: causes and metabolic consequences. *Nat. Rev. Endocrinol.* 2015;11(12):701–711.

267. **Valdearcos M, Xu AW, Koliwad SK.** Hypothalamic inflammation in the control of metabolic function. *Annu. Rev. Physiol.* 2015;77:131–160.
268. **Moullé V-S, Picard A, Le Foll C, Levin B-E, Magnan C.** Lipid sensing in the brain and regulation of energy balance. *Diabetes Metab.* 2014;40(1):29–33.
269. **Adams AC, Kharitonenkov A.** FGF21: The center of a transcriptional nexus in metabolic regulation. *Curr. Diabetes Rev.* 2012;8(4):285–293.
270. **Bae K-H, Kim J-G, Park K-G.** Transcriptional regulation of fibroblast growth factor 21 expression. *Endocrinol. Metab. Seoul Korea* 2014;29(2):105–111.

Figure 1. Comparison of major anatomical expression sites of FGF21 in mice and humans. The most prominent expression sites are highlighted by using bold fonts. The intensity of expression is indicated by font/picture size. Brackets: skeletal muscle FGF21 expression signals were found in mice already in the basal state, in humans only upon hyperinsulinemia. Figure was produced using Servier Medical Art (http://www.servier.com).

Figure 2. Regulation of hepatic FGF21 production in mice and men. Data on signaling and nuclear/transcriptional factors (see reviews (269,270)) are mainly derived from genetic mouse studies and cell culture systems. Stimulatory effects are indicated by plus (+), the inhibitory effects by minus (-). Stimuli/mediators in mice and humans are blue, stimuli/mediators that are different between mice and humans are red and stimuli/mediators with only mice data available are black. ER – endoplasmic reticulum; FFA – free fatty acids. Figure was produced using Servier Medical Art (http://www.servier.com).

Figure 3. Regulation of extrahepatic production and circulating FGF21 in mice and men. Stimulatory effects are indicated by plus (+), the inhibitory effects by minus (-). Stimuli rendering extrahepatic tissues as source of circulating FGF21 levels are indicated in blue. ER – endoplasmic reticulum; FFA – free fatty acids. Figure was produced using Servier Medical Art (http://www.servier.com).

Figure 4. FGF21 effects on metabolism in mice and men. Stimulatory effects are indicated by plus (+), the inhibitory effects by minus (-). Effects that are similar in mice and humans are indicated in blue, effects that are different between mice and humans (or controversial in the literature) are indicated in red and effects for which human data are missing are black. Figure was produced using Servier Medical Art (http://www.servier.com).

Figure 1

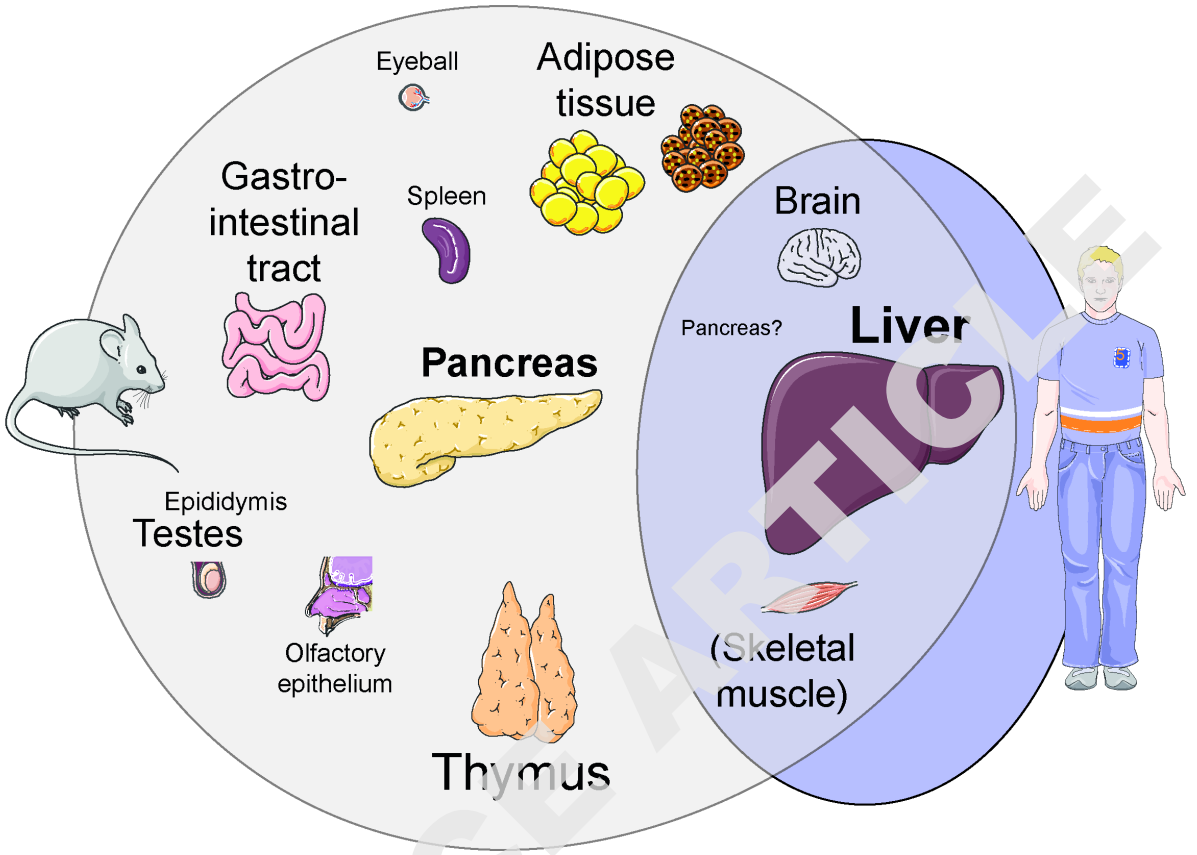

Figure 2

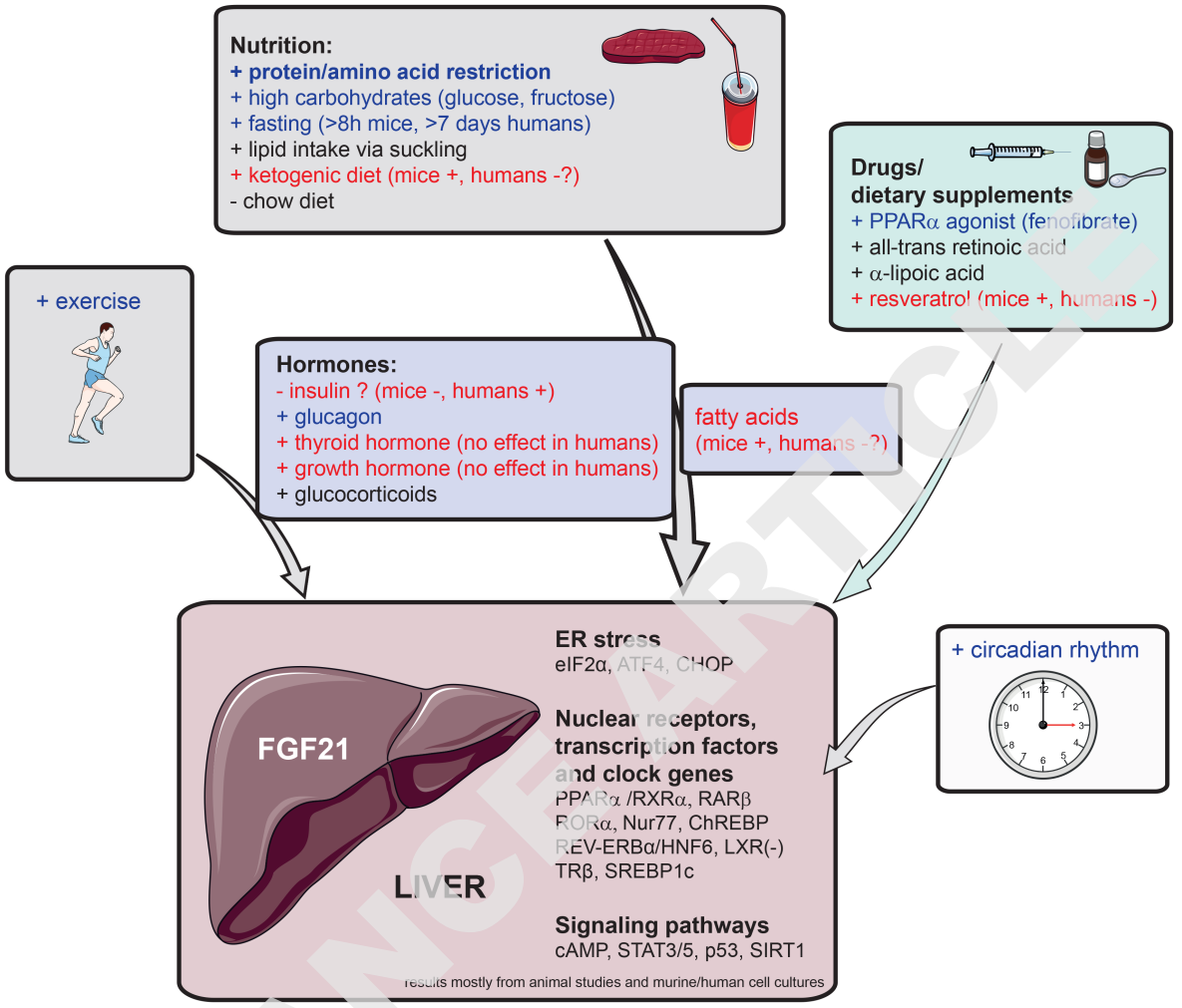

Figure 3

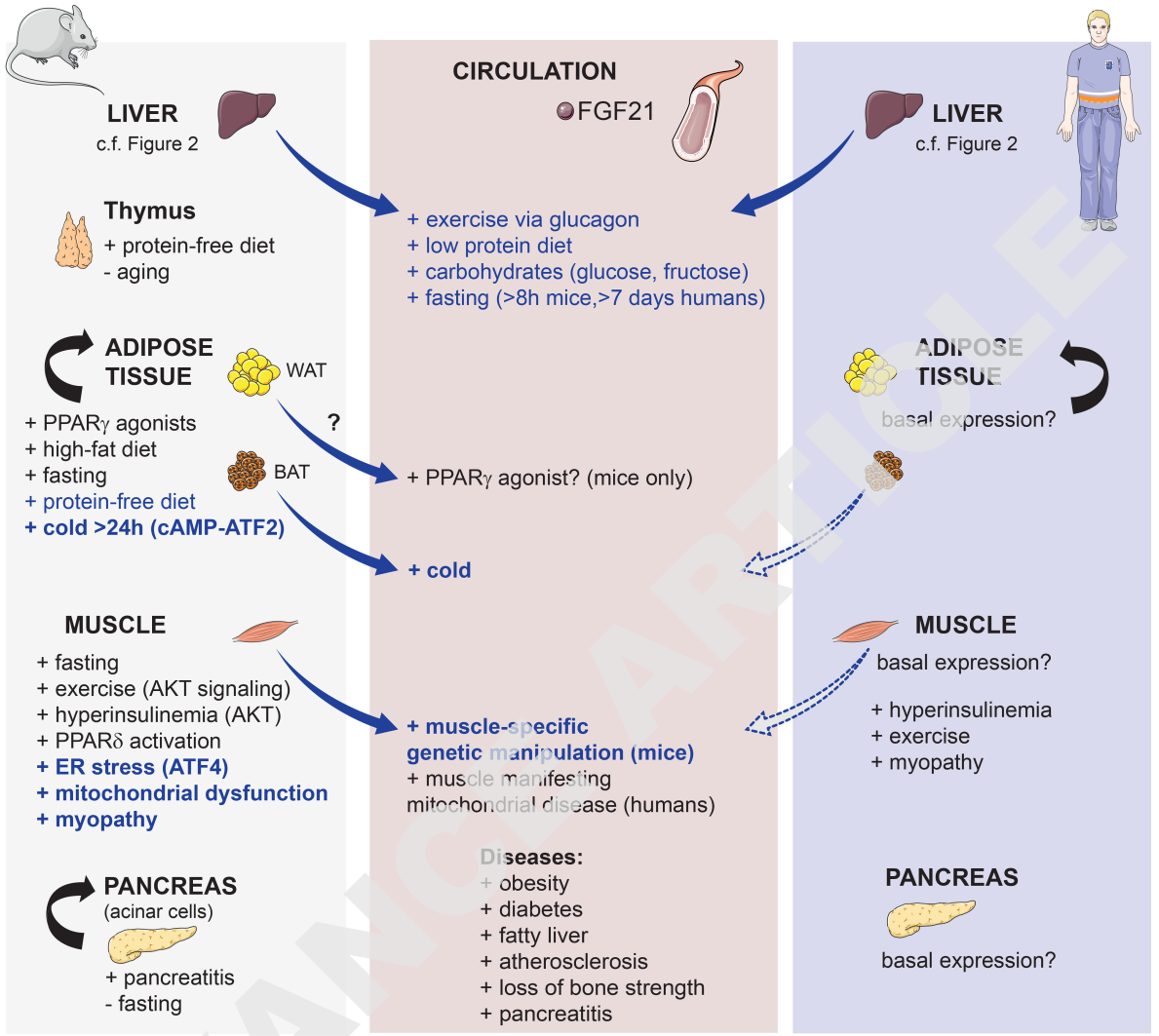

Figure 4