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Abstract

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FGF15/19 from mice to humans

Fibroblast Growth Factor 15/19 – From Basic Functions to Therapeutic Perspectives

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Discovered 20 years ago, Fibroblast Growth Factor (FGF) 19, and its mouse ortholog FGF15, were the first members of a new subfamily of FGFs able to act as hormones. During fetal life, FGF15/19 is involved in organogenesis, affecting the development of the ear, eye, heart and brain. At adulthood, FGF15/19 is mainly produced by the ileum, acting on the liver to repress hepatic bile acid synthesis and promote postprandial nutrient partitioning. In rodents, pharmacologic doses of FGF19 induce the same anti-obesity and anti-diabetic actions as FGF21, these metabolic effects being partly mediated by the brain. However, activation of hepatocyte proliferation by FGF19 has long been a challenge to its therapeutic use. Recently, genetic reengineering of the molecule has resolved this issue. Despite a global overlap in expression pattern and function, murine FGF15 and human FGF19 exhibit several differences in terms of regulation, molecular structure, signaling and biological properties. As most of the knowledge originates from the use of FGF19 in murine models, differences between mice and humans in the biology of FGF15/19 have to be considered for a successful translation from bench to bedside. This review summarizes the basic knowledge concerning FGF15/19 in mice and humans, with a special focus on regulation of production, morphogenic properties, hepatocyte growth, bile acid homeostasis, as well as actions on glucose, lipid and energy homeostasis. Moreover, implications and therapeutic perspectives concerning FGF19 in human diseases (including obesity, type 2 diabetes, hepatic steatosis, biliary disorders and cancer) are also discussed.

ESSENTIAL POINTS

- Human Fibroblast Growth Factor (FGF)19 and its mouse ortholog FGF15 are gut-derived circulating hormones (enterokines) which repress hepatic bile acid synthesis and change their composition, through the FGF receptor 4 and the co-receptor β-Klotho (KLB) complex.
- FGF15/19 is involved in the early development of ear, eye, heart and brain during organogenesis, as well as in muscle growth at adulthood.
- Mouse FGF15 and human FGF19 exhibit differences in terms of regulation, molecular structure, signaling and biological actions, implying a careful interpretation of data originating from the use of FGF19 in murine models.
- In rodents, pharmacologic doses of FGF19 induce similar anti-obesity and anti-diabetic effects as FGF21.

- Some of the metabolic effects of FGF15/19 appear to be mediated by the brain.
- Stimulation of hepatocyte proliferation represents the main risk to use of FGF19 as a drug, but this effect can be overcome by genetic reengineering of the molecule.
- In addition to obesity and type 2 diabetes, FGF19 can also be a therapeutic target in type 1 diabetes, in diseases associated with bile acid over-production and in hepatocellular carcinoma.

1. Introduction

Overweight and obesity, caused by unhealthy eating and reduced physical activity, are rapidly rising worldwide with the consequence of increasing the prevalence of type 2 diabetes (T2D) (1, 2). Obesity, T2D and related insulin resistance are associated with complications involving angiopathies and nerve damages, but also liver-related diseases (3). Nonalcoholic fatty liver disease (NAFLD) is the most common hepatic disorder related to obesity and T2D (4, 5). A subset of NAFLD patients develop a state of hepatic inflammation [Nonalcoholic steatohepatitis (NASH)], which can progress to fibrosis, cirrhosis and ultimately result in hepatocellular carcinoma (HCC) (6). Apart from lifestyle changes including weight loss and physical activity, there is currently no efficient long-term drug to improve and/or avoid development and progression of obesity, T2D and NAFLD.

Fibroblast growth factors (FGFs) form a large family of more than 20 signaling molecules with pleiotropic functions in different areas of biology (7). FGFs bind and signal through four membrane tyrosine kinase receptors [Fibroblast growth factor receptors (FGFRs1-4)] (8-10). The FGFRs present the same overall structure, with an extracellular ligand binding domain (composed of three immunoglobulin-like domains), a transmembrane domain, and an intracellular tyrosine kinase domain (8-10). Splice variants for FGFR1, FGFR2 and FGFR3 exhibit differential binding selectivity for FGFs while no splice variants are known for FGFR4 (8). FGFs also bind components of the extracellular matrix such as heparan sulfate and heparan sulfate proteoglycan (11, 12). This interaction increases the stability and affinity of FGFs for FGFRs and limits their diffusion within the local environment (11, 12). In fact, FGFs classically signal through a paracrine manner, especially between epithelium and mesenchyme (13). FGFs and FGFRs present highly specific expression patterns, determining selectivity of their sites of action (7). Moreover, the expression of FGFs and FGFRs is temporally-regulated. Some FGFs are mainly expressed during development while others are more involved in adult tissues homeostasis (7).

For many years, investigations concerning FGFs mainly focused on proliferation, migration and differentiation processes, in particular in the field of developmental biology (7). The recent discovery of a new subgroup of FGFs, namely endocrine FGFs, has stimulated medical research in the field. Although FGF15/19, FGF21 and FGF23, the three endocrine FGFs, present different structures and functions, they all bind poorly to heparin and derivatives (14). This allows these FGFs to diffuse beyond the interstitial space to reach the bloodstream and act far from their tissue of origin, as classical endocrine hormones (15). In this way, FGF23 derived from bone acts on the kidney to regulate phosphate re-absorption and vitamin D production, representing an important endocrine loop in the control of mineral homeostasis (16). FGF21, mainly produced by the liver during metabolic stress, regulates numerous metabolic processes, including glucose and lipid homeostasis. Thus, it represents an interesting candidate for treatment of obesity and T2D (17).

The present review will deal with FGF19 and its mouse ortholog FGF15, with particular focus on the regulation of its production, its physiological and pharmacological actions, as well

as its involvement in human diseases and potential use in the treatment of metabolic and gastro-intestinal diseases. As much of the basic knowledge in the field of FGF15/19 biology comes from murine studies, species differences in the functions of FGF15/19 between rodents and humans will also be highlighted in a translational perspective.

2. Molecular biology of FGF15/19

2.1. FGF15/19 gene and protein

Murine FGF15 was initially identified as a downstream target of the chimeric oncoprotein E2A-Pbx1 in the NIH3T3 cell line (18). The FGF15 gene is located on chromosome 7 and consists of 3 exons. The FGF15 protein, composed of 218 amino acids, is the most divergent among the known FGF family members (18). Subsequent screening of expressed sequence tags led to the discovery of FGF19 cDNA from human neuroepithelial cells showing sequence homology with the corresponding region of mouse FGF15 (19). The chromosomal location of FGF19 was found to be chromosome 11q13.1, a genetic region associated with an osteoporosis-pseudoglioma syndrome (20). The whole FGF19 coding region revealed a complete protein sequence of 216 amino acids sharing 51% of similarity with mouse FGF15 (19). The homology between the human FGF19 and mouse FGF15 was significantly less than that observed between most human and mouse FGF orthologs (19), explaining their divergent names. However, based on the evolutionary conservation of the CCND1-ORAOV1-FGF19-FGF4 locus from zebrafish to human, it was concluded that the human FGF19 gene was the ortholog of the murine FGF15 gene (21).

2.2. FGF15/19 structure and affinity for receptors/co-receptors

Compared to other FGFs, the key heparin-binding sites of FGF19 have radically different conformations and charge patterns (22, 23). Particularly, the conformation of the heparin-binding region between beta-strands 10 and 12 in FGF19 diverges completely from the analog region of paracrine-acting FGFs (15). A cleft between this region and the beta1-beta2 loop (the other heparin-binding region) precludes direct interaction between FGF19 and heparin/heparan sulfate (15), reducing the heparin-binding affinity and facilitating the endocrine function (15). These conformational predictions are confirmed by *in vitro* experiments showing little or no affinity of FGF19 for heparan sulfate/heparin (24).

The co-receptor β-Klotho (KLB) has emerged as a compensatory mechanism for the poor ability of heparin/heparan sulfate to promote binding of FGF19 to cognate receptors (15). KLB is a single pass membrane protein consisting of two internal repeats with homology to family 1 glycosidases (25). Crystal structures of KLB extracellular regions reveal that its glycosidase substrate-binding domain has evolved to recognize a sugar-mimicking Ser-Pro-Ser motif present in FGF19 (26). Use of chimeric proteins developed from members of the endocrine FGF subfamily and Klotho family identified the C-terminal tail of FGF19 as being required for KLB recognition and signaling (27). Interestingly, FGF15 possesses a unique unpaired cysteine (cys-135) which permits dimerization of monomers and is absent in FGF19 and all other endocrine FGFs (28). This structural feature can explain functional divergence from the human FGF19.

FGF19 exhibits a high specificity for FGFR4 binding (20). Unique sequences in both FGF19 and FGFR4 are key to the formation of the complex, offering a conformational explanation for this unusual selective affinity (22). Different amino acids at both the N- and C-termini of FGF19 contribute to full FGFR4 activation (29). Nevertheless, amino acid residues 38-42 of FGF19 are sufficient to confer FGFR4 activation to other endocrine FGFs (30).

Whether FGF15/19 can directly interact with FGFR4 in the absence of KLB remains controversial and possibly concentration-dependent (31-33). Whilst FGFR4 is only activated by FGF19 among endocrine FGFs, FGF19 can also bind and signal through other FGFRs. In fact, FGF19 binds FGFR1 with comparable affinity to FGFR4 in the presence of KLB (34). Furthermore, FGF19 can signal through FGFR1-3 bound by KLB (35-37), especially at a supra-physiological concentration (33). In addition, each FGFR isoform (originating from splice variants) has a different affinity for KLB. FGFR1c and FGFR4 bind KLB more potently than FGFR2c or FGFR3c while type b isoforms of FGFRs fail to interact with KLB (35). In consequence, FGFR isoform composition also impacts FGF15/19 binding to KLB-FGFR complexes.

In contrast to the wide distribution of FGFRs in the body, the pattern of Klotho protein expression is more limited (38) and defines the main tissue targets of endocrine FGFs. In mice, FGFR4 gene is highly expressed in kidney, liver, lung and adrenal, while KLB expression is high in enterohepatic tissues (liver, gallbladder, colon, pancreas) and white adipose tissue (WAT)/brown adipose tissues (BAT) (38). The liver is the only organ in which FGFR4 and KLB are abundantly co-expressed (31, 35, 38) and is in consequence the main target tissue of FGF15/19. In line with this concept, early response genes are only induced in the liver of FGF19-injected mice (31). FGF19 can also signal through FGFRs associated with Lactase-like Klotho (38). However the biological relevance of this signaling complex remains unknown.

2.3. FGF15/19 intracellular signaling pathways

FGFs mediate their cellular responses by the binding and activation of FGFR1-4 (9, 10). FGF/FGFR interaction induces receptor dimerization, activation and auto-phosphorylation of multiple tyrosine residues in the cytoplasmic domain (9, 10, 39).

Most of the knowledge concerning intracellular events mediating FGF15/19 actions comes from *in vitro* work involving various cell lines. In transfected HEK293, L6, 3T3-L1 and Caco-2 cell lines, FGF19 induces phosphorylation of FGFR substrate 2 alpha (FRS2α) and extracellular signal-regulated kinase (ERK1/2) (31, 35, 40, 41). FGF19 also activates the mammalian target of rapamycin complex 1 (mTORC1)-p70S6K and ERK-p90RSK pathways independently to regulate S6 in an additive manner in hepatoma cells and in 3T3-L1 adipocytes (42). FGF19 signals to mTORC1 through Ras-like (Ral) protein to regulate gene expression in HepG2 cells (42). FGF19 signaling through FGFR4 phosphorylates the inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)-kinase subunit beta (IKKβ) in HEK293 and DU145 cell lines, inhibiting inflammation through the downregulation of NFκB (43). Beyond phosphorylation cascades, FGF19 stimulates the transcription of early response genes (c-Fos, JunB and c-Jun) in HepG2 and Hep3B cell lines (31). FGF19 also increases Small Heterodimer Partner (SHP) protein stability by inhibiting its ubiquitination and proteasomal degradation (44). Finally, in primary cultures, FGF19 activates the c-Jun N-terminal kinase (JNK) pathway in human hepatocytes (45), induces phosphorylation of Forkhead Box O1 (FoxO1) in mouse hepatocytes (46) and increases the phosphorylation of signal transducer and activator of transcription 3 (STAT3) in rat hepatocytes (47).

Intracellular signaling downstream of FGF15/19 has also been investigated *in vivo*. Acute FGF19 administration induces phosphorylation of ERK1/2 (35, 48) and c-Fos expression (31) in mouse liver. The phosphorylation of ERK1/2, as well as several other signaling events triggered by FGF15/19, such as the activation of ribosomal S6 kinase (p90RSK), SHP upregulation and Protein Kinase C (PKC)s phosphorylation, appears dependent on the presence of the non-receptor tyrosine phosphatase with two Src-homology 2 domains (Shp2) in mouse liver (49).

Shp2 forms a complex with FRS2α and Gab1 upon FGF19 stimulation (49). Chronic FGF15 overexpression increases the hepatic phosphorylation of both FoxO1 and protein kinase B (Akt) (46). FGF19 also increases the phosphorylation of eIF4B, eIF4E, rpS6, FRS2α, ERK, p90RSK, Glycogen Synthase Kinase (GSK)3α and GSK3β in mouse liver (48). Importantly, FGF19 equally induces hepatic STAT3 phosphorylation (50-52). Administration of FGF19 to mice also activates the phosphorylation of the ERK1/2 signaling pathway in extra-hepatic tissues including adipose tissue (35), the hypothalamus (53) and the ileum (41).

It should be noted that concentrations of FGF15/19 used in these *in vitro* and *in vivo* studies can be several orders of magnitude higher than the maximal circulating values observed in animals or humans, even postprandially or following pharmacologic/nutritional stimulation. Although higher levels of FGF15/19 can be present in the portal circulation compared to the systemic blood circulation, one should be cautious concerning direct translation of the basic signaling studies to human physiology. The main intracellular signaling pathways mediating FGF15/19 actions in hepatocytes are illustrated in Figure 1.

3. Production of FGF15/19

3.1. Tissue specificity of FGF15/19 expression

During murine development, the FGF15 gene is predominantly expressed in the nervous system, the pharyngeal pouches, and the tail bud (18). FGF15 expression first appears at embryonic day (E)7.5 in the mouse neuroectoderm before exhibiting a highly dynamic expression pattern during brain development (18). In the diencephalon, strong FGF15 expression is initially seen in the dorsal thalamus before the extension to the ventral thalamus (18). In the mesencephalon, FGF15 is firstly expressed caudally before being predominantly observed rostrally at later developmental stages (18). In the telencephalon FGF15 is detected in the olfactory bulb region (18). FGF15 expression is also detected in the inner cell layer of the optic cup, in the rostral hindbrain regions (rhombomeres 1 and 3), in the caudal hindbrain, in the cervical spinal cord and in the terminal rostral hypothalamus (18, 54). In contrast, during adulthood, FGF15 globally disappears from the central nervous system (38), although recent work found FGF15 expression in specific neurons of the dorsomedial hypothalamus and the perifornical area (55). Instead, the FGF15 gene is highly expressed in the ileum (distal part of the intestine) and also detected in the jejunum and duodenum (more proximal intestine segment) of adult mice (38, 56). At the cellular level, FGF15 expression is detected in the enterocytes of the villus epithelium with highest expression in the intervillus regions (56). Little or no FGF15 is observed in the ileal crypts or lamina propria (56). Of note, FGF15 expression in the ileum is weaker during gestation and lactation in mice and rats (57-59). In the pig intestine, expression of FGF19 begins soon after birth but achieves maximal expression in the ileum during adulthood (60).

In the human fetus, *in situ* hybridization and RT-PCR analyses reveal FGF19 expression in brain, skin, cartilage, inner retina, small intestine, kidney, as well as placental villi and the umbilical cord (20). FGF19 is also expressed in human embryonic stem cells, and expression levels correlate positively with the undifferentiated state (61). In adulthood, FGF19 expression is detected in biopsies from human ileum, but not in biopsies from human colon (62). FGF19 is not detected basally in human liver. Nevertheless hepatic expression can be induced during cholestasis or cirrhosis (63, 64). Non-parenchymal cells, notably cholangiocytes (the cells lining the bile duct) largely contribute to FGF19 expression in the cholestatic liver (63). In addition, stimulated human hepatocytes also exhibit FGF19 induction *in vitro* (65). Finally, FGF19 is also

expressed in human gallbladder epithelial cells (20, 66). This expression appears even more abundant than in the ileum (67, 68).

In summary, while FGF15 expression is restricted to the distal part of the intestine in adult mice, gallbladder and cholestatic liver also express FGF19 in humans. A comparison of FGF15 and FGF19 expression patterns in mice and humans is illustrated in Figure 2.

3.2. FGF15/19 secretion

FGF15 accumulates in a time-dependent manner in the media of cells infected with an FGF15-expressing adenovirus, revealing the secretion of the protein (56). However, FGF15 is a weak antigen, and detection of FGF15 in the blood has long been problematic, questioning its real endocrine action (69). Initially, FGF15 was not detected in the rat portal circulation using mesenteric perfusion, suggesting a low level of production/secretion or a high lability of the protein (70). Moreover, FGF15 protein levels in the portal blood do not match with the marked increase in FGF15 expression observed in the stimulated ileum (71). Nevertheless, an essay by stable isotope standards and capture by anti-peptide antibodies (SISCAPA), combining immuno-enrichment with mass spectrometry has overcome this issue (72). This new dosage technique shows that i) FGF15 circulates in plasma, ii) in a regulated manner, iii) at concentrations that are known to activate its receptor, and iv) in strong correlation with ileal gene expression (72).

Compared to FGF15, immunological methods for detection (RIA- or ELISA-based assays) of FGF19 are more reliable, which has allowed the observation of a wide inter-individual variation of concentration in human circulation (median 115 pg/ml, variation 7.4-fold) (69). Circulating FGF19 levels appear to be unrelated to age or gender in healthy humans (73, 74). However, other studies show that circulating FGF19 surges more than 10-fold in early infancy from infra- to supra-adult concentrations (75). However, this induction is reduced in small-for-gestational-age infants (75). Surprisingly, centenarians also exhibit increased FGF19 levels, independently associated with their successful aging (76). As FGF19 is mainly produced by the ileum, a primary delivery is expected in the portal circulation. In this way, portal levels of FGF19 are higher than arterial levels (77). A net release of FGF19 by the portal-drained viscera can be calculated under fasted steady state conditions, while no significant flux of FGF19 can be measured across the liver (77). This suggests that most intestine-derived FGF19 binds to hepatocytes or the hepatic extracellular matrix during the first pass through the liver and does not substantially reach peripheral tissues, at least at the same concentration. Surprisingly, human bile contains 20 to 100 times more FGF19 than the systemic circulation (67, 68). The likely sources of biliary FGF19 are the gallbladder and the extrahepatic bile duct, both exhibiting high expression levels of FGF19 (20, 66).

In the gallbladder epithelium, FGF19 protein is present in cytoplasmic granules similar to secretory vesicles (67). The role of this exocrine secretion is unknown and the impact of gallbladder-derived FGF19 on the circulating pool remains elusive. In fact, the lowering effect of BA sequestrants on serum FGF19 levels rather suggests a limited contribution of tissues other than the ileum (67).

3.3. Regulation of FGF15/19 production

Molecular regulators

As with other endocrine FGFs, FGF15/19 is transcriptionally regulated by nuclear receptors. Farnesoid X receptor (FXR) is the classical nuclear receptor for bile acids (BAs) (78, 79). FGF19 is the most induced gene in human hepatocytes treated with the FXR synthetic agonist, GW4064, or the BA, chenodeoxycholic acid (CDCA) (45). The FGF19 gene contains functional FXR

responsive elements within the second intron (45) and in the promoter region (80). Analogously, rat and mouse FGF15 genes contain FXR-responsive elements in intron 2 (81) and FGF15 gene expression is dramatically increased in the intestine following GW4064 administration (56, 81). Intestine-specific FXR-deficient mice show a strong downregulation of FGF15 expression in the ileum (82), while transgenic mice expressing a constitutively active FXR in the intestine present an increased FGF15 expression in this tissue (83). The FXR-mediated transcriptional activation of FGF19 is negatively regulated by Sterol Regulatory Element Binding Protein 2 (SREBP-2) in human intestinal cells (84). In turn, FGF19 increases functional interaction between SHP and SREBP-2, leading to repression of SREBP-2 target genes (85).

Pregnane X receptor (PXR) is another nuclear receptor whose primary function is to sense exogenous toxic substances, leading to the upregulation of detoxification proteins (86). Highly hydrophobic BA, such as lithocholic acid (LCA), can also bind PXR (87). Overexpression of PXR and stimulation with its ligand rifampicin lead to a significant activation of the proximal FGF19 promoter region in a human adenocarcinoma cell line (88). In contrast, PXR appears to regulate negatively FGF15 expression in mice (89). The promoter region of FGF19 also possesses a functional amino-acid-response element (AARE), responsible for enhancing transcription through Activating Transcription Factor 4 (ATF4) in response to Endoplasmic Reticulum (ER) stress (90). Induction of FGF19 is also observed after silencing release through blockade of methyl-cytosine-phosphate-guanine (CpG)-binding domain proteins in HeLa cells (91). Furthermore, FGF15 gene expression can be induced in colonic myofibroblasts through inhibition of miR-710 by carbon monoxide treatment (92).

The FGF15 gene can also be repressed by transcription factors. Krüppel-like factor 15 (KLF15) binds the FGF15 promoter at multiple consensus binding sites and represses FGF15 expression independently of BAs (93). Overexpression of KLF15 in primary small intestinal epithelial mouse cells potently represses FGF15 gene expression, while knockdown of KLF15 induces FGF15 expression (93). The transcription factor GATA4 represses FGF15 transcription within the proximal intestine and limits its expression to the ileum (94). This inhibition occurs through both indirect mechanisms (modification of BA uptake and FXR gene expression) and direct binding to a consensus GATA4 regulatory element in intron 2 of the FGF15 gene (94).

In addition to transcriptional regulation, FGF15 concentration seems to be controlled at the post-transcriptional level. Indeed, the protein Diet1 co-localizes and interacts with FGF15 to enhance its production levels via both transcriptional and post-transcriptional mechanisms (95). Diet1-deficient mice have reduced ileal FGF15 levels (96). The regulation of FGF15/FGF19 production in mice and humans, including transcriptional regulators involved, is summarized in Figure 3.

In addition to the direct regulation of its production, the action of FGF15/19 can be modulated through the tuning of its co-receptor KLB. In this way, FXR activation also primes the liver for FGF15/19 signaling through hepatic induction of KLB expression (97). In contrast, microRNA-34a inhibits KLB expression and attenuates hepatic responses to FGF19 (98). In the same way, interleukin (IL)-1 beta (IL-1β) specifically inhibits KLB expression and FGF19 signaling in the liver (99) while tumor necrosis factor (TNF)-alpha (TNF-α) represses KLB expression in adipose cells (100). Finally, as KLB is the obligate co-receptor for both FGF21 and FGF15/19, FGF21 overexpression antagonizes FGF15/19 binding to the KLB/FGFR4 receptor complex in mouse liver (101).

Bile acids (BAs)

As endogenous ligands for FXR, BAs are the prototypical inducers of FGF15/19. In consequence, the modification of their concentrations and/or composition in the small intestine directly impacts FGF15/19 production. Four days of diet containing cholic acid (CA) increases FGF15 expression in the mouse ileum (56). In contrast, administration of BA sequestrants (resins binding BA and preventing their reabsorption from the intestine) causes a steep decrease in ileal FGF15 gene expression in mice (82, 102). Of note, BA species have different impacts on the expression of FGF15. Oral supplementation with CA or deoxycholic acid (DCA) increases the ileal expression of FGF15 at lower doses and to a higher extent than CDCA or LCA in mice (103). Conversely, oral supplementation with ursodeoxycholic acid (UDCA) does not induce FGF15 expression in the ileum (103). Co-administration of tauro-beta-muricholic acid (MCA) (T-βMCA) attenuates T-CA-induced FGF15 expression in germ-free mice (104), in line with the antagonist action of T-βMCA on FXR evidenced in this study. Nevertheless, the ability of orally administered BA to stimulate FGF15 in mice intestine only partially matches their agonistic activity on FXR (CDCA>DCA>LCA≫CA) (105), possibly due to chemical conversion of the ingested BAs (as for example the bioconversion of CDCA into MCA in rodents). Moreover, beyond the specific ability of BA to activate the FXR receptor, trans-epithelial transport of BA is also a key step in the regulation of FGF15/19 production. Inhibiting apical versus basolateral BA transport in the ileum results in opposite regulation of FGF15. In fact, FGF15 expression is strongly elevated in the ileum of mice deficient in the basolateral BA transporter organic solute transporter alpha (Ostα) (106), while it is reduced in the ileum of mice deficient for the apical sodium-dependent BA transporter (ASBT) (107, 108).

In humans, both feeding (109) and intra-duodenal infusion (110) of CDCA increase circulating FGF19 levels. Conversely, administration of UDCA to obese patients for three weeks reduces their circulating FGF19 levels (111). Basal circulating FGF19 levels are also reduced following treatment with BA sequestrants in patients (109, 112-114). After cessation of treatment, FGF19 displays rebound increases above baseline levels (114). In contrast, BA sequestrants in colonic-release pellets fail to regulate FGF19 levels (115). The selective ileal BA transporter inhibitor A4250 decreases circulating FGF19 levels by 70% as soon as 4h after administration (116). In human ileal explants, FGF19 expression is strongly induced by CDCA, Glyco(G)-CDCA and CA, but DCA and LCA are significantly less potent (62). In human primary hepatocytes, all BAs increase FGF19 gene expression, the rank orders of FGF19 induction being CDCA ≈ CA > DCA ≈ LCA > UDCA (117, 118). The semi-synthetic BA analogue obeticholic acid also increases FGF19 secretion through FXR-activation in human primary hepatocytes (119, 120) and in Caco-2 cells in which it is more potent than G-CDCA (121).

Gut microbiota/antibiotics

The crosstalk between microbiota and the intestine wall, as well as the ability of gut microbiota to transform BA through various chemical processes (such as deconjugation and dehydroxylation), suggest that the gut microbiota can be a key player in the regulation of FGF15/19. This was first proven by the use of antibiotics. Administration of non-absorbable antibiotic cocktails (ampicillin or bacitracin/streptomycin/neomycin) significantly decreases FGF15 expression in mouse ileum (104, 122), in association with dampening of FXR signaling (123). A compensatory increase in BA import and FGF15 expression can be observed in regions of the proximal small intestine in parallel with the decrease observed in the ileum following antibiotic exposure (124). Antibiotic-mediated repression of FGF15 gene can be prevented by supplementation with T-DCA or CA, but not with T-CA or βMCA (122, 125). This suggests that

stimulation of FGF15 gene expression by gut microbiota is due to its ability to deconjugate T-CA into CA, which then adequately activates FXR signaling (125). In line with this concept, FXR and FGF15 levels are higher in the ileum of conventionally raised mice compared to germ-free mice (104). In turn, colonization of germ-free mice with mouse microbiota induces expression of FGF15 in their ileum while the induction is delayed after colonization with a human microbiota (126). The microbiota-induced upregulation of FGF15 in the ileum is abolished in FXR-deficient mice (104).

Moderate changes in gut microbiota through the administration of prebiotics or probiotics impact less consistently FGF15 expression in mice. Administration of the antioxidant tempol reduces the proportion of *Lactobacillus* (and its important bile salt hydrolase activity responsible for the deconjugation process). This leads to the accumulation of intestinal T-βMCA (an FXR antagonist) and reduction of FGF15 expression in mouse intestine (127), corroborating studies using antibiotics. In contrast, supplementation with the VSL#3 probiotic (comprising several strains of Lactobacillus and Bifidobacterium) shifts gut microbiota and enhances BA deconjugation but represses ileal FGF15 expression (128). Resveratrol administration, which enriches gut microbiota in *Lactobacillus* and *Bifidobacterium*, also decreases ileal FGF15 production (129). Chronic ethanol treatment, associated with an overrepresentation of bacteria deconjugating BA and thus an increased amount of unconjugated BA in the intestine, dampens FGF15 secretion (130). The supplementation with *Lactobacillus rhamnosus* in High-Fat Diet (HFD)-fed mice does not induce any change in intestinal FGF15 expression (131). Together, these results suggest that the presence of gut microbiota is required for physiological BA deconjugation allowing a normal FGF15 expression. Nevertheless, enrichment of gut microbiota with species harboring a high BA deconjugating activity does not allow positive regulation of FGF15. Finally, pathogenic bacteria can also regulate FGF15. Indeed, infection with Salmonella or intravenous administration of Listeria both trigger a significant reduction in the intestinal expression of FGF15, but surprisingly, this occurs independently of any damage to the ileal enterocyte layer (132).

Macro- and micronutrients

Both chronic imbalance of diet composition in mice and acute administration of a single type of macronutrient in humans impact FGF15/19 production.

Consumption of a HFD stimulates FGF15 expression in mouse ileum (133). Palmitic acid induces FGF15 gene expression in mouse ileum and also induces FGF19 expression in human hepatocytes (134). Although the ingestion of lipids triggers BA release, the FGF19 secretion profile during a lipid tolerance test in humans remains uncertain (135, 136).

A sucrose-rich diet also induces the expression of FGF15 in mouse ileum (108). In healthy humans, the ingestion of carbohydrates induces the most rapid and highest increase in circulating FGF19 levels compared to other macronutrients (136). Since carbohydrate intake exerts little effect on global circulating BA levels, the underlying mechanism could be related either to a modification in BA composition (impacting FXR activation) or another pathway independent of the BA/FXR axis (136). Nevertheless, neither glucose nor insulin seems to mediate the rise in FGF19 secretion since their postprandial levels were not associated with the FGF19 response (136). The FGF19 increment after oral glucose loading is positively associated with age, and negatively associated with abnormal glucose regulation (137). The drop in circulating CDCA levels in patients with isolated-impaired fasting glucose could explain their lower FGF19 secretion during a glucose tolerance test (138).

FGF15 expression is not changed in the ileum of mice fed a leucine-deficient diet for one week (139). Ileal FGF15 expression is increased in rats fed with soy proteins compared to rats fed with casein (140). However, the addition of cholesterol to the soy protein diet is sufficient to repress FGF15 production (140). In healthy humans, protein intake induces a modest and delayed elevation of FGF19 when compared to levels observed after carbohydrate ingestion (136).

In a one-month dose-response study evaluating undernutrition, only the most severe caloric restriction (40% reduction of daily food intake) tends to increase FGF15 gene expression in the mouse ileum (141). This upregulation appears to be caused by the increased intestinal BA content (in particular more hydrophobic BAs) (141). In humans, few data regarding the impact of caloric restriction are available, but higher FGF19 levels are reported in children suffering from severe acute malnutrition (142).

Fat soluble vitamins stimulate both FGF15 and FGF19 transcription, but species differences are observed in terms of nuclear receptors involved in this process. In fact, receptors for vitamin A and D induce the expression of the FGF15 gene through distinct cis-acting response elements in the promoter and intron of the FGF15 gene. Transactivation of both response elements appears to be required to maintain basal FGF15 expression levels *in vivo* (143). In mice, induction of FGF15 by vitamin D is mediated through vitamin D receptor (VDR) independently of FXR, while the induction of FGF15 by vitamin A is mediated through the retinoid X receptor (RXR)/FXR heterodimer, independently of BA (143). In human intestinal cell lines, vitamin A derivatives induce FGF19 transcription (144). In contrast to mouse FGF15, this direct regulation is FXR-independent and mediated by RXR/RAR heterodimer acting on a DR-5 element (144).

Classically known to stimulate FGF23 production, the availability of inorganic phosphate (Pi) inversely impacts FGF15 production. In fact, dietary Pi restriction up-regulates FGF15 expression in mouse ileum, but not in VDR-deficient mice (145). Conversely, high Pi-fed mice have significantly lower transcript levels of FGF15 in the ileum (146).

Circadian rhythm

In mice, circadian analyses reveal the highest FGF15 expression in the ileum at the end of the dark phase (feeding period for rodents) and the lowest FGF15 expression at the end of the light phase (resting period for rodents) (82, 93). A strong correlation between ileal FGF15 expression and circulating FGF15 levels is observed across the day in mice (72). Maximal ileal expression and circulating FGF15 levels were observed in the middle of the light phase in this study (72). The transcription factor KLF15 is directly involved in the circadian control of FGF15. In fact, KLF15-deficient mice lose the daily pattern of FGF15 production with increased levels at multiple time points across a 24 h cycle (93).

The circadian pattern of FGF15 production driven by food consumption in mice is quite analogous to that observed for FGF19 in humans. In fact, circulating FGF19 levels exhibit a pronounced diurnal rhythm in humans, with peaks occurring 90-120 min after the postprandial rise in serum BA (109). Moreover, the rhythmicity of circulating FGF19 is abolished upon fasting (109) and altered following cholecystectomy (68), highlighting regulation by the trans-intestinal BA flux.

Intestinal/hepatic diseases models

The expression of FGF15 has also been investigated in the intestine of various mouse models mimicking human diseases of the digestive system. Ileal FGF15 expression is decreased in mice with Dextran Sulfate Sodium (DSS)-induced colitis (147). This change is due to overactivation of intestinal peroxisome proliferator-activated receptor (PPAR)α-UDP-glucuronosyltransferases

(UGTs) axis, which promotes the metabolic elimination of BAs in enterocytes (147). In contrast, DSS-treated mice with ileum-sparing colitis show higher circulating FGF15 levels (148). IL-10-deficient mice with ileitis have a trend toward decreased circulating FGF15 levels compared with controls (148). Mice suffering from colitis-associated cancer, exhibiting a concomitant decrease in FXR agonists and antagonists BAs in the ileum, have repressed FGF15 expression in the ileum (149). Mice with acute cerulein-induced pancreatitis also exhibit a reduction of ileal FGF15 expression (150).

Liver diseases models also interfere with normal FGF15 expression in the gut. Mice with chemically-induced cholestatic liver injury, exhibit a reduction of FGF15 expression in the ileum (151). In contrast, hypercholanemic organic anion-transporting polypeptide (OATP) and sodium-taurocholate cotransporting polypeptide (NTCP)-deficient mice present increased FGF15 expression, in line with observations in mice treated with a specific NTCP inhibitor (152). Mice overexpressing the bile salt export pump (ABCB11) also show strongly elevated FGF15 expression levels in the ileum (153). Mice with hepatocyte-specific expression of a dominant stable form of β-catenin exhibit severe cholestasis and high ileal FGF15 expression levels (154).

Surgical procedures

Bariatric surgery, such as Roux-en-Y gastric bypass, vertical sleeve gastrectomy and gastric banding, cause substantial weight loss and are now popular treatments for obesity (155-157). Beyond the decrease in body weight, these surgical procedures induce substantive metabolic changes, notably affecting FGF15/19 levels.

Gastric banding consists of the placement of a silicone ring around the stomach to create a small upper gastric pouch at the bottom of the oesophagus (155-157). An initial report showed no significant change for basal circulating FGF19 levels after gastric banding compared to preoperative values (158), while more recent studies report a decrease (159) or a continuous increase (160). Postprandial circulating FGF19 concentration increases after laparoscopic adjustable gastric banding (161).

In the Roux-en-Y gastric bypass (RYGB), a small gastric pouch is created, draining alimentary bolus into the jejunum (alimentary limb), which causes nutrients to bypass the pylorus and duodenum (157). Early and late observations after RYGB surgery reveal that fasting circulating levels of FGF19 are elevated compared to preoperative values (158, 162-164). Circulating FGF19 levels also increase after biliopancreatic diversion (159) and after implantation of a duodeno-jejunal bypass liner excluding the duodenum and proximal jejunum from contact with ingested food (165). The rise in FGF19 seems directly related to the surgery since no change is observed in subjects who achieve similar improvements in glycemic control (164) or weight loss (166) by conventional dietary treatment. The postprandial peak of FGF19 also occurs earlier and reaches a higher value in RYGB patients (161, 167). Nevertheless, other studies show no change in fasting FGF19 levels acutely or until 1 year after RYGB (168), or report non-significant trends of increased in FGF19 levels from pre-surgery to 2 years post-surgery (169). One possibility is that surgery can change FGF19 levels in only some patient subsets. In fact, no change in circulating FGF19 levels is detected in RYGB patients exhibiting normal pre-operative glucose tolerance, while low levels of FGF19 observed in diabetic patients gradually increase after RYGB surgery (170).

Sleeve gastrectomy consists of the creation of a long, thin, longitudinal gastric pouch or sleeve, reducing the volume of the stomach by approximately 70-80%, but leaving the pylorus intact (157). Fasting and postprandial FGF19 levels increase after sleeve gastrectomy (171-176),

possibly in line with changes in BA composition observed after this surgical procedure (173). Circulating FGF19 also increases after laparoscopic greater curvature plication (159).

Surgical procedures also regulate FGF15 in rodents. In mice, ileocecal resection leads to the upregulation of FGF15 expression in the ascending colon, but this compensation is absent in germ-free mice and in FXR-deficient mice (177). After bile flow diversion through gallbladder anastomosis to the ileum, FGF15 gene expression is repressed more than 2-fold in the ileum, despite a massive increase in circulating BAs (mainly the FXR antagonist T-βMCA and T-ωMCA) (178). Repopulation of mouse liver with human hepatocytes strongly induces FGF15 expression in the ileum (179). In rats, ileal interposition (surgical relocation of the distal ileum into the proximal jejunum) causes a robust induction of FGF15 (180). Vagotomy changes BA composition and increases passive absorption of BAs leading to induction of FGF15 in the rat intestine (181).

4. Role of FGF15/19 in development and cellular growth/proliferation

4.1. Effects on fetal tissues

Several members of the FGF family act in the early stages of embryonic development and during organogenesis to maintain progenitor cells and mediate their growth, differentiation, survival, and patterning (10). In addition to its endocrine functions, FGF15/19 is also involved in numerous developmental processes, mainly evidenced in the chick, zebrafish or mouse embryo. Survival of mice deficient in FGF15 depends on the genetic background. Under the C57Bl/6/129/Sv hybrid background, FGF15 KO mice are mostly embryonic lethal, since less than 2% of the homozygous mice can survive (182). In contrast, under a 129SvJ background, FGF15 KO mice are viable and fertile (183).

Otic development

From the earliest stages of development, the FGF19 gene is expressed in anatomic regions involved in inner ear development in the chick (184). As a mediator of the mesodermal signal, FGF19 synergistically interacts with Wnt-8c (mediating neural signals) to initiate inner ear development (185). The FGF19 gene is induced in the mesoderm by FGF8 originating from the endoderm, and in turn, FGF19 stimulates neural ectoderm to express signals promoting the otic placode (186). FGF19 signaling is required to initiate a proliferative progenitor region that is a precursor of both the inner ear and the neurogenic epibranchial placodes (187).

Mouse FGF15 KO embryos do not have otic abnormalities at E9.5-E10.5 (182). Unlike FGF19, FGF15 is not expressed in the mesoderm underlying the presumptive otic placode, but is expressed in the adjacent neurectoderm (182). This suggests that during otic induction, FGF19 signals in either an autocrine fashion to the mesoderm or a paracrine fashion to the neurectoderm, whereas FGF15 signals in an autocrine fashion to the neurectoderm (182).

Eyes development

In the developing chick, FGF19 is expressed in the retina, the optic vesicle, lens primordia, the retinal horizontal cells (188), and more acutely, in the post-mitotic neuroblasts during their migration from the ventricular surface to their final location (189). During the last third of embryogenesis, FGF19 expression in the retina is progressively down-regulated, and is no longer detected at one month of life (189). FGF19/FGFR4 signaling interplays with FGF8 signaling and the L-Maf transcriptional system to regulate early lens development (190).

In zebrafish embryos, the transcription factor FOXC1 induces FGF19 expression in corneal and periocular mesenchymal cells (191). Loss of FGF19 results in anterior segment structures

within the eye (191) and a size reduction of the lens and the retina (192). FGF19 is involved in cell survival but not in cell proliferation during embryonic lens and retina development (192).

In the pig, FGF19 is expressed in adult retinal pigment epithelial cells and impacts proliferation/survival in photoreceptors (193). In mice, FGF15 is also expressed in the optic vesicle, a subset of progenitor cells of the neural retina, emerging ganglion and amacrine cells during retinogenesis (188).

Brain development

In the zebrafish, FGF19 is expressed in the forebrain, midbrain and hindbrain, and is involved in cell proliferation and cell survival during embryonic brain development (194). FGF19 appears essential for the specification of gamma-aminobutyric acid (GABA)ergic interneurons and oligodendrocytes generated in the ventral telencephalon and diencephalon (194). In the forebrain, FGF19 expression is down-regulated on inhibition of Hedgehog signaling (194).

In mice, FGF15 is expressed from early neurulation in various zones of the neural tube including the isthmus, the intra-thalamic zona limitans and the anterior neural ridge (195). FGF15 is initially present in domains where FGF8 is also expressed and, at later stages, in specific groups of neural cells (196). In the diencephalon and midbrain, FGF15 regulates proliferation and survival of dorsal cell populations by regulating the ability of dorsal neural precursors to respond to dorsally secreted Wnt mitogens (197). FGF15 is directly regulated by sonic hedgehog signaling through the GLI zinc-finger transcription factors (198, 199). Studies using FGF15 KO mice reveal that FGF15 suppresses proliferation, promotes neuronal differentiation and caudoventral fate (200), showing opposite effects to FGF8 on neocortical patterning and differentiation. In FGF15 KO mice, dorsal midbrain neural progenitors fail to exit the cell cycle and to generate the requisite number of post-mitotic neurons due to altered expression of differentiation helix-loop-helix transcription factors (201). In fact, the expression of Id1, Id3, and Hes5 is strongly increased and ectopically expanded, while the expression of Ascl1, Neurog1, Neurog2, Neurod1 is strongly decreased in the dorsolateral midbrain of FGF15 KO mice compared to wild-type mice (201). Moreover, FGF15 KO embryos exhibit a strong reduction of FGFR3 expression in the alar pre-thalamus, associated to a high proliferation rate of thalamic progenitors and disruption of thalamic neurogenesis (202). FGF15 is a direct target of miR-302 in the fetal neural tube and FGF15 overexpression is sufficient to drive precocious neural differentiation (203, 204).

In humans, FGF19 could also harbor morphogenic properties in the brain, as suggested by its ability to promote spontaneous generation of dorsoventrally polarized neural-tube-like structures at the level of the cerebellum in tridimensional embryonic stem cell culture (205).

Heart development

In mice, FGF15 is detected in the developing pharyngeal arches, a region important for correct development of the aortic arch and cardiac outflow tract (206). FGF15 KO mice present early morphological abnormalities of the outflow tract due to aberrant behavior of the cardiac neural crest, resulting in heart defects consistent with misalignment of the aorta and pulmonary trunk (206). In this context, FGF15 operates through a pathway independent of Tbx1, a master regulator of pharyngeal arches development (206). Homology in the enhancers of the FGF15 and FGF19 promoters suggests that FGF19 is also involved in the early development and distribution of cardiac neural crest cells, being a candidate gene for congenital heart defects in humans (207).

4.2. Effect on hepatocyte growth and proliferation

First evidence of a role for FGF19 in hepatocyte growth comes from phenotypic observations in FGF19 transgenic mice who developed locally invasive hepatocellular carcinoma (HCC) tumors by 10 to 12 months of age (208). Hepatocellular proliferation, predominantly observed in pericentral hepatocytes, precedes tumor development (208). Similarly, acute FGF19 administration also increases hepatocellular proliferation (208). Furthermore, FGF19 delivery through adeno-associated virus (AAV) induces highly proliferative liver tumors with a latency depending upon the mouse genetic background (50). Hepatocarcinogenesis in FGF19 transgenic mice can be prevented by monoclonal antibodies selectively blocking the interaction of FGF19 with FGFR4 (209) or by genetic FGFR4 deficiency (210). These results strongly suggest that FGFR4 mediates the oncogenic effect of supra-physiologic levels of FGF19. In accordance, molecular studies with truncated mutants of FGF19 and with FGF19/FGF21 chimeric molecules also identify the FGF19/FGFR4 interaction as the mechanism driving hepatocyte proliferation and HCC (29, 30).

Additional studies revealed the molecular and cellular mechanisms underlying FGF19-induced oncogenicity. *In vivo*, as soon as 12h after a single administration of FGF19, the expression of key proteins known to drive cell proliferation (such as transforming growth factor-beta-induced protein ig-h3, vascular cell adhesion molecule 1, annexin A2 and vigilin) are induced in mouse liver (51). *In vitro*, FGF19 induces the expression of the epidermal growth factor receptor (EGFR) ligand amphiregulin, which participates in the induction of the cycle cell regulator cyclin D1 (211). FGF19 increases the invasive capabilities of human HCC cell lines by promoting epithelial-mesenchymal transition via a GSK3β/β-catenin pathway (212, 213).

Moreover, FGF19 facilitates cell survival through a resistance to apoptosis, involving GSK3β activation and nuclear accumulation of Nrf2 (214). FGF19 increases the STAT3 protein level and its phosphorylation (51). This action is central to the proliferative properties of FGF19. In fact, a modified FGF19 unable to induce STAT3 phosphorylation presents no mitogenicity and no induction of pro-oncogenic target genes (50). In contrast to FGF19, long-term overexpression of FGF15 does not induce HCC in db/db and diet-induced obese (DIO) rodent models (28). Again, this is also due to the absence of upregulation of STAT3 target genes in livers of mice overexpressing FGF15 (28). The hepatocellular ablation of STAT3 blocks the initiation and progression of FGF19-dependent HCC formation (52). In vivo and in vitro observations suggest a non-cell-autonomous activation of STAT3 by FGF19 (52) and identify IL-6 originating from immune/Kupffer cells as a key intermediate relaying the pro-tumorigenic activity of FGF19 in mice (52).

Several therapeutic approaches have been used to dampen the oncogenic FGF19/FGFR4 signaling pathway. Functionally, clonal growth and tumorigenicity of HCC cells can be inhibited by knockdown of FGF19 through RNA interference, small hairpin RNA or neutralizing anti-FGF19 antibodies (215, 216). Anti-FGFR4 monoclonal antibody inhibits tumor growth in mice bearing the HUH7 liver cancer cell line xenograft (210). BLU9931, a selective and irreversible small-molecule inhibitor of FGFR4, shows antitumor activity in mice with an HCC tumor overexpressing FGF19 (217). The selective covalent FGFR4 inhibitor, H3B-6527, tested in a large panel of HCC cell lines and patient-derived xenografted mouse models, shows that FGF19 expression is a predictive biomarker for its response (218). Cancer cell lines harboring a gain of FGF19 copy number and a concomitant expression of KLB are sensitive to selective FGFR inhibitor NVP-BGJ398 (219). ASP5878, an inhibitor of FGFR1-4, potently suppresses the growth of several FGF19-expressing hepatocellular carcinoma cell lines and induces sustained tumor regression in xenografted mouse models (220). Nevertheless, the strategy of inhibiting the

FGF19/FGFR4 pathway in HCC carries intrinsic safety risks. This represents a translational challenge with questions about the degree of blockade to achieve therapeutic benefits without inducing adverse hepatic/gastro-intestinal toxicity in humans (221). Anti-FGF19 antibody demonstrated dose-related liver toxicity and severe diarrhea in a safety study in cynomolgus monkeys (222). The side effects seem to be related to increased BA synthesis, change in the expression of BA transporters in the liver and ileum, and enhanced BA enterohepatic recirculation (222).

The blockade of elevated FGF19 levels or the inhibition of overactivated FGFR4 signaling could present valuable anti-oncogenic properties. Nevertheless, FGF15/19 signaling can stimulate liver regeneration in case of increased demand. FGF15 administration promotes liver repair in mouse models of chemical liver injury or partial hepatectomy (223), even improving survival after extensive hepatectomy (224). An FGF19/apolipoprotein A-I chimaeric molecule reduces liver injury and enhances regeneration in acetaminophen-intoxicated or hepatectomized mice (225). Conversely, the lack of endogenous FGF15 can also be deleterious in situations of regenerative need. FGF15 KO mice have extensive liver necrosis due to reduced hepatocyte proliferation and impaired cell cycle progression (183). After administration of carcinogens, FGF15 KO mice present attenuated hepatocellular proliferation and fibrogenesis compared to wild-type mice (226). FGF15 KO mice show more advanced liver injury (and mortality depending on genetic background) following partial hepatectomy (183, 224) or acetaminophen overdose (227). Of note, even if the down-regulation of FGF15/19-FGFR4 signaling can directly dampen hepatocyte regeneration, it can also have deleterious consequences for liver integrity through derepressed BA synthesis. Thus, liver alterations in FGF15 KO mice are accompanied by persistently elevated intrahepatic BA levels (224). siRNA-mediated knockdown of FGFR4 also causes necrotic damage due to intrahepatic overload of BAs (in particular of T-CA) following partial hepatectomy (228). Accumulation of BA in the liver in the context of FGF15/FGFR4 inhibition could result from an imbalance between constitutive BA overproduction exceeding export capabilities. Another explanation could be a change in BA transporters which are tightly controlled by hepatic FXR activity, itself dependent on BA composition.

Progression of liver HCC caused by FXR deficiency can be prevented by the reactivation of intestinal FXR, normalizing the FGF15 axis and BA homeostasis (229). As for FGF15/19, BAs are also key players of the hepatostat (adjustment of liver size to the physiological need) (230), delineating direct and indirect (BA-mediated) actions of FGF15/19. In this way, enhanced growth of livers of mice with humanized hepatocytes, which do not recognize FGF15, is due mainly to increased BA synthesis (63). Nevertheless, mice overexpressing FGF15 present very low BA levels but show increased hepatocyte proliferation in basal conditions and a further induction of cell-cycle progression genes after partial hepatectomy (231). This demonstrates that FGF15 is critical in the phases of priming and termination of liver regeneration, independently of BA levels (231).

4.3. Effect on skeletal muscle growth

FGF signaling is an important regulator of myogenesis (232-234), but the involvement of endocrine FGFs in this process was long been unrecognized. A recent report revealed a role for FGF19 in the regulation of skeletal muscle mass (235). Treatment with FGF19 causes skeletal muscle hypertrophy in mice leading to a better muscle strength (235). Hypertrophy is not related to the numbers or the type of muscle fibers, but to a shift toward larger myofibers (235). In human myoblasts, FGF19 does not affect cell proliferation or the expression of classical

myogenic factors, but increases the size of myotubes (235). Muscular signaling in response to FGF19 stimulation includes the phosphorylation of ERK1/2 and the ribosomal protein S6 kinase (S6K1) (235). Interestingly, FGF19 ameliorates skeletal muscle atrophy in obese and aged-mice as well as in mice treated with glucocorticoids (235), and therefore represents a promising strategy for increasing skeletal muscle mass in various human pathological conditions. Of note, FGF21 is devoid of muscular anabolic action and muscle-specific KLB-deficient mice are refractory to the hypertrophic effect of FGF19 (235). Thus, FGF19 should act through the KLB/FGFR4 complex in skeletal muscle, in line with previous reports involving FGFR4 in myogenesis (236-238).

5. Role of FGF15/19 in metabolism

5.1. Effect on liver and gallbladder

Bile acids homeostasis

BAs are amphiphatic molecules produced by the liver from cholesterol through two distinct synthesis pathways. In the classic (neutral) pathway, cholesterol 7α-hydroxylase (CYP7A1) is the rate-limiting and major regulatory enzyme (239, 240). Later steps involve sterol 12α-hydroxylase (CYP8B1) leading to synthesis of CA while other enzymes can alternately produce CDCA (239, 240). In the alternative (acidic) pathway, cholesterol is only converted to CDCA (239, 240). CDCA is more hydrophobic than CA but is rapidly metabolized into highly hydrophilic MCAs in rodents, but not in humans (239, 240). All the primary (liver-derived) BAs are conjugated with taurine or glycine to enhance their solubility and represent the main organic compounds of bile, secreted by the liver into the gallbladder for interprandial storage (239, 240). Meal consumption triggers the release of bile into the duodenum to allow emulsification and digestion of dietary lipids. BAs are actively reabsorbed in the ileum, and return to the liver through the portal circulation, thus following an entero-hepatic circulation (239, 240). The few primary BAs escaping active ileal reuptake reach the colon and are metabolized by gut microbiota into secondary BAs (for example by dehydroxylation of CA into DCA), which are passively absorbed by the colon or eliminated in the feces (239, 240). Beyond their role in lipid assimilation, BAs have hormonal actions throughout the body. Notably, BA bind and activate several receptors, mainly nuclear FXR and membrane TGR5 (GPBAR1) BA receptors, both central regulators of glucose and lipid homeostasis (240, 241).

As biological detergents, BAs can be toxic and their production needs to be tightly regulated. In the hepatocyte, FXR acts as the main BA sensor in charge of a negative feedback, limiting BA production (78, 79). Thus, CYP7A1 is overexpressed in FXR-deficient mice (242). A series of experiments has revealed that FGF19 is central in the control of BA production. FGF19 expression is strongly induced by BA in human hepatocytes and in turn, treatment with FGF19 reduces the level of CYP7A1 expression (45, 65). In the same way, mice overexpressing FGF19 present low CYP7A1 expression and reduced BA production (45, 243). These observations initially suggested a hepatic autocrine/paracrine role for FGF19 in the repression of BA production. Similarly, FGF15 is also involved in the negative feedback of BA synthesis. FGF15 administration decreases CYP7A1 mRNA levels in wild-type but not in FGFR4 KO mice (56). Both FGF15 KO, FGFR4 KO and KLB KO mice present elevated BA production due to upregulation of CYP7A1 in the liver (56, 244-246). Further studies have highlighted the central role of the intestine in the negative feedback model. Notably, ileal FGF15 expression negatively correlates with hepatic CYP7A1 expression in bile duct-ligated mice (56). Moreover, the FXR agonist GW4064 significantly represses hepatic CYP7A1 expression in liver-specific FXR-

deficient mice, but not in intestine-specific FXR-deficient mice (247). This demonstrates that activation of FXR in the ileum, and subsequent FGF15 release, is required for short-term CYP7A1 repression. Of note, CYP8B1 expression is more dependent on direct negative feedback by hepatic FXR than intestinal FXR-FGF15/19 (247, 248). The role of FGF19 in the ileo-hepatic negative feedback of BA synthesis is also supported by clinical observations. A postprandial increase in BA levels triggers FGF19 secretion, which is followed by a decrease in BA synthesis (109). Moreover, both primary BA malabsorption (249) and ileal resection (250) reduce FGF19 levels and increase BA synthesis.

Beyond the regulation of the global level of BA production, ileo-hepatic FGF15-19/FGFR4/KLB negative feedback also impacts BA composition. FGF19 infusion in mice shifts BA synthesis from the neutral to the alternative pathway, reducing the ratio of CA/CDCA (29). Analogously, FGF19 injections increase the ratio of MCA/CA in mouse bile, inducing a more hydrophilic BA pool (251). Treatment with the intestinal FXR agonist fexaramine induces enteric FGF15 and leads to increases in LCA (a secondary BA derived from CDCA), at the expense of T-CA (252, 253). Nevertheless, this latter observation requires further confirmation since substantial amounts of LCA in mouse plasma are not reported in others studies (104, 127, 251, 254-256).

On the contrary, mice with intestinal-FXR deficiency exhibit very low FGF15 expression levels, an increased proportion of CA and DCA and a decreased proportion of β- and ω-MCA in bile (82). This leads to a rise in the BA hydrophobicity index compared to wild-type mice (82). Mice with hepatocyte-specific KLB deficiency exhibit an increased fraction of CA in their BA pool (72). In the same way, global KLB KO mice exhibit a shift in BA production (255). This modification is highlighted by activation of the classical BA synthesis pathway at the expense of the alternative pathway (255). This leads to a predominant representation of CA and DCA among circulating BAs (255). Similarly, in humans, BA sequestrants decrease FGF19 levels and result in a preferential increase in CA synthesis at the expense of CDCA (112). Taken together, these observations show that FGF15/19 negative feedback shifts BA synthesis from the neutral to the alternative BA synthesis pathway, both in mice and humans. In rodents, this results in a more hydrophilic BA pool due to the conversion of hydrophobic CDCA into highly hydrophilic MCA. In contrast, in humans, this generates a more hydrophobic BA pool. Conversely, attenuation/abrogation of FGF15/19 signaling enriches the BA pool in 12α-hydroxylated BAs such as CA or DCA. This results in a relatively more hydrophobic BA pool in rodents and a more hydrophilic BA pool in humans (CA being more hydrophilic than the persistent CDCA). In consequence, FGF15/19 signaling can change not only BA levels, but also BA species distribution. Therefore, modification in the composition of the BA pool also impacts the intracellular signaling through the BA receptors FXR and TGR5.

As a gatekeeper of BA production, FGF19 can represent a therapeutic opportunity to treat diseases related to BA dysregulation. However, the proliferative action of FGF19 on hepatocytes represents a major risk to treating hepato-biliary disorders. To overcome this therapeutic limitation, molecular reengineering of the FGF19 molecule allows dissociation of the proliferative and metabolic properties of the molecule. The genetically modified FGF19 M70 carries three amino acid substitutions (A30S, G31S, and H33L) and a 5-amino acid deletion. This FGF19 variant exhibits the same biological activity as FGF19, including FGFR4 binding, ERK signaling and suppression of CYP7A1, without tumorigenicity (50). M70 protects mice from liver injury induced by either extrahepatic or intrahepatic cholestasis (50, 257). AAV-mediated delivery of M70 rapidly attenuates liver injury, inflammation, biliary fibrosis, and

cholelithiasis in mice deficient for the canalicular phospholipid flippase (MDR2 KO mice) (258). The hepatosplenomegaly and ductular proliferation associated with cholangiopathy are also improved with M70 administration (258). From a translational point of view, M70 potently reduces circulating levels of 7α-hydroxy-4-cholesten-3-one (C4) in healthy volunteers (257). This reflects a dampening of CYP7A1 activity in humans with the perspective of treating disorders of BA dysregulation (257). To date, M70 (also named NGM282) is the only FGF19 analogue tested in clinical trials in patients suffering from primary biliary cirrhosis and diabetes (259).

Gallblader filling

Another main function of FGF15/19 in BA homeostasis relates to the filling of the gallbladder. The gallbladder of FGF15 KO mouse is almost devoid of bile and administration of FGF15 or FGF19 causes a >10-fold increase in gallbladder volume, without changing bile flow rate (260). A weaker stimulatory action of FGF15/19 in the filling of gallbladder is also observed in wild-type mice (260). As no FGF15 expression is detected in the liver, gallbladder, common bile duct, or sphincter of Oddi, this suggests that ileal-derived FGF15 acts as a hormone to stimulate gallbladder filling in mice (260). The gallbladder volume is also reduced in FGFR4 KO mice but to a lesser extent than in FGF15 KO mice, suggesting that other FGFRs contribute to the actions of FGF15 on the gallbladder (260). In the same way, gallbladder volume is reduced in KLB KO mice, which exhibit a resistance to gallstone formation (245). Postprandial circulating cholecystokinin (CCK) concentrations are lower in FGF15 KO mice compared to wild-type mice, demonstrating that this classic bile releasing factor is not involved in the action of FGF15 (260). In contrast, FGF15 completely blocks contraction of the gallbladder caused by CCK (260). FGF15 and FGF19 stimulate gallbladder filling at least in part by causing a cAMP-dependent relaxation of gallbladder smooth muscle (260). In humans, after CDCA administration, a progressive increase over time in both FGF19 levels and gallbladder volume is observed both in control subjects and in patients with intestinal diseases (261).

The high concentration of FGF19 in human bile (67, 68), originating from the gallbladder itself and the extrahepatic bile duct (20, 66), contrasts with the absence of FGF15 in mouse bile. The role of this exocrine secretion remains poorly studied. It has been suggested that biliary FGF19 can protect against detrimental effects of BAs or regulate mucin expression in tissues exposed to concentrated bile (67). This action can explain species differences since mice, devoid of biliary FGF15, have a less toxic/hydrophobic BA composition than humans.

Nutrient partitioning in postprandial and fasted states

In response to BA and nutrients reaching the intestine during digestion, FGF15 gene expression gradually increases in the mouse ileum, peaking around 1 h post-gavage (262). In humans, circulating FGF19 concentration peaks 2-3 h following a meal (109, 249), with an approximate half-life of 30 minutes (263). This food-driven pattern of regulation suggests that FGF15/19 can act as a hormone of the fed-state. In fact, administration of FGF19 significantly increases protein synthesis and glycogen accumulation in the liver of fasted mice (48). In contrast, fed FGF15 KO mice have half the hepatic glycogen stores of wild-type mice (48). This effect of FGF15/19 is similar to, but independent of, insulin action. In fact, postprandial peak of FGF15 levels is delayed compared to the insulin peak (262). In addition, insulin increases hepatic FGFR4 levels (46), suggesting a priming of FGF19 action. Both hormones work in a coordinated, temporal fashion to facilitate the proper storage of nutrients after a meal (48). Even if FGF15 signaling decreases FoxO1 activity, as does insulin (46), the intracellular signaling pathways used by FGF19 and insulin show differences. FGF19 activates the Ras/ERK1/Mnk1/p90RSK pathway,

while insulin signals through PI3K/Akt/mTOR/p70S6K, allowing overlapping but distinct biological actions for both hormones (48).

Unlike insulin, FGF19 does not acutely increase hepatic triglycerides in postprandial state, thus uncoupling carbohydrate and lipid storage (48). Furthermore, in rat primary hepatocytes, FGF19 suppresses the expression of lipogenic enzymes and represses the insulin lipogenic action (through increasing STAT3 activity and decreasing PPAR-gamma coactivator 1 beta (PGC-1β) expression) (47). In fasted mice, injection of FGF19 decreases the expression of proteins involved in fatty acid synthesis and increases the expression of proteins involved in fatty acid oxidation (51). FGF15/19 also inhibits the expression of one carbon cycle genes, critical determinants of hepatic lipid levels (264), and mediates postprandial epigenetic repression of hepatic autophagy (265).

In addition to its action during the fed-state, FGF15/19 suppresses hepatic metabolic pathways, which are active during fasting, including gluconeogenesis and the tricarboxylic acid cycle flux (262). This hepatic action is mediated through decrease of the activity of transcription factor cAMP regulatory element-binding protein (CREB) and downregulation of PGC-1α and its gluconeogenic/oxidative target genes (262). In accordance, FGF15 KO mice and FGFR4 KO mice exhibit increased gluconeogenesis and higher glycaemia than wild-type mice after refeeding (262).

Hepatic lipid storage

The concomitant role of FGF15/19 in the control of BA production and nutrient partitioning raises questions about its long-term effects on hepatic lipid metabolism. FGF19 transgenic mice present a reduced expression of lipogenic enzymes and triglyceride content in the liver (266). Treatment with the long-lasting FGF19/apolipoprotein A-I chimaeric molecule also reduces liver lipid accumulation *in vivo* and protects hepatocytes against ER stress and cytotoxicity induced by palmitic acid *in vitro* (134). In mice fed a high-fat, high-fructose, high-cholesterol diet, reengineered FGF19 M70 reduces hepatic levels of toxic lipid species (diacylglycerols, ceramides and free cholesterol) and increases levels of unoxidized mitochondrial cardiolipins (267). In line with a FGF15/19-mediated repression of liver fat storage, FGF15 KO mice also exhibit exacerbated hepatic steatosis when fed a HFD (134) while other studies only report an attenuation of fibrosis in the same context (268). Of note, one to two weeks of FGF19 administration transiently increase circulating triglycerides and cholesterol levels in *ob/ob* mice and in DIO mice (269). This action is also observed with a modified FGF19 (269), only activating FGFR4, and could be directly related to the inhibition of BA production. In fact, treatment with BA binding resins (270, 271), as well as CYP7A1 deficiency (272), increase triglycerides levels. However, this effect remains transitory, suggesting that it is gradually overcome by the more chronic extrahepatic lipid-lowering action of FGF19 (269).

Taken together, these results suggest that activation of the FGF15/19 signaling pathway present potential opportunities with respect to hepatic steatosis. Nevertheless, the abrogation of endogenous FGF15 signaling does not result in an inverse hepatic fat overload. In fact, both FGFR4 KO mice and KLB KO mice exhibit few modifications of hepatic lipid content on a chow diet, and are resistant to hepatic steatosis on a HFD (246, 255, 273, 274). A possible explanation for this protection can be the modification in BAs levels/composition. In fact, mice overexpressing CYP7A1 present a similar pattern of BAs as KLB KO mice and exhibit the same resistance to hepatic steatosis (275). The underlying mechanisms could involve changes in FXR signaling in the liver (known to repress *de novo* lipogenesis (276)) or activation of TGR5 signaling in BAT (driving thermogenic lipid use) (255). Thus, if FGF15/19 signaling presents

direct anti-lipogenic actions in the long-term, its blockade also leads to attenuation of hepatic lipid storage through the modification of the BA pool. Of note, FGF19 can also interfere with the secretory function of the liver, regulating the expression of its sister molecule FGF21 (277), as well as anti-atherogenic and atherogenic proteins (278-280).

5.2. Effect on whole body energy and glucose homeostasis

Several genetic and pharmacological studies in mice have demonstrated the beneficial action of FGF15/19 in energy balance. Transgenic mice overexpressing FGF19 are leaner than wild-type mice, exhibiting decreased fat content despite higher food intake (266). This phenotype is explained by higher oxygen consumption (with no change in the respiratory quotient, reflecting the proportion of carbohydrates and lipids used), and is also associated with an increased insulin sensitivity (266). FGF19 overexpression also confers resistance to DIO and can alleviate the genetic obesity in *ob/ob* mice, partly due to the increase in BAT activity (243). AAV delivery of FGF15 and FGF19 also allows investigation of their global metabolic actions. Both FGF15 and FGF19 overexpression reduce fat mass and increase energy expenditure in DIO mice, but FGF19 appears more potent (28). FGF19 overexpression, but not FGF15 overexpression, reverses diabetes in db/db mice (independently of weight loss) (28). Moreover, endogenous FGF15 does not influence body weight homeostasis through extra-hepatic action. In fact, hepatocyte-specific KLB KO mice present high FGF15 levels, but gain similar weight to wild-type mice on a HFD (281). As with genetic overexpression, short-term (one week) pharmacologic administration of FGF19 exerts systemic metabolic actions. IV administration of FGF19 (1 mg/kg) increases the metabolic rate and fat oxidation in mice on HFD, without modifying food intake (243). Treatment with IP FGF19 (1 mg/kg) reduces body weight and enhances glucose utilization in both DIO and ob/ob mice (37, 243). The improved glycaemia obtained through SC FGF19 infusion (1mg/kg) occurs independently of any change in body weight in *ob/ob* mice (269).

Taken together, these metabolic observations suggest that FGF19 represents an interesting candidate for treatment of obesity and T2D. Modified forms of FGF19 have also dissociated its effects on lipid and glucose metabolism. FGF19 (FGF19-4) retains the ability to stimulate glucose uptake *in vitro* and *in vivo* in ob/ob mice without inducing FGFR4-mediated hepatocyte proliferation (282). FGF19v, which activates KLB/FGFR1c, but not KLB/FGFR4, reduces blood glucose levels and therefore improves glucose tolerance (29). Similarly, FGF19-7, presenting a preferred selectivity for FGFR1c, is equally effective as wild-type FGF19 in regulating glucose, lipid, and energy metabolism in DIO and *ob/ob* mice (283). In contrast, FGF19dCTD, which activates only FGFR4, but not FGFR1c, -2c, or -3c, represses BA synthesis, but fails to improve glucose levels and insulin sensitivity in *ob/ob* mice (32). Moreover, infusion of FGF19 at supra-physiological levels improves glucose tolerance (independently of body weight) to a similar extent in wild-type and FGFR4 KO mice, indicating that FGFR4 is not required for glucose lowering (29). Together, these results demonstrate that in contrast to the repression of BA synthesis mediated through FGFR4, the glucose lowering action of (pharmacologic) FGF19 is mediated by FGFR1. Other studies revealed that the glucose lowering action of FGF19 involves FGFR1 expression, not in the adipose tissue (284), but rather in the central nervous system (281).

5.3. Effect on brain impacting body energy and glucose homeostasis

Numerous gut-derived hormones act on the central nervous system to elicit their metabolic effects, including the control of food intake, energy expenditure and glucose tolerance (285, 286). This suggests a possible involvement of FGF15/19 in the metabolic gut-brain axis. In contrast to specific uptake of FGF19 in the liver, influx of FGF19 into mouse brain is non-linear, non-saturable and affected by its blood concentration (287). Peripheral delivery of FGF19

triggers ERK signaling in the hypothalamus (53). FGFR1 and FGFR4 are both present in rat hypothalamus (288). KLB is also expressed in the mouse hypothalamus (in particular in the suprachiasmatic and paraventricular nuclei), in the hindbrain (in the area postrema and the solitary nucleus) and in the nodose ganglia of the periphery (289, 290). Together, these nuclei expressing KLB include the dorsal-vagal complex, a major integrative center for the autonomic nervous system (291). Although of primary interest, these observations in murine studies require caution regarding their translation to humans.

The first evidence of a brain-mediated FGF19 metabolic activity comes from central injections of FGF19 into the lateral ventricle in mice, which produce an increase in the metabolic rate comparable to systemic administration (243). This observation is confirmed by central FGF19 delivery, which stimulates sympathetic outflow to BAT and increases energy expenditure (281). Moreover, studies involving genetically modified mice also support a central action for FGF19. In fact, mice harboring KLB deficiency in the CNS are refractory to body weight and glycaemia improvements induced by FGF19, while mice with hepatocyte- or adipose-specific KLB deficiency remain sensitive to FGF19 action (281).

Mechanistically, some studies suggest that central FGF15/19 signaling interferes with neuronal control of insulin and glucagon secretion, while other studies highlight a role in the hypothalamic-pituitary-adrenal (HPA) axis or glucose effectiveness (insulino-independent glucose use).

ICV FGF19 injections for four days reduce body weight and improve both glucose-induced insulin secretion and insulin sensitivity in DIO mice (53). This involves activation of ERK1/2 signaling and repression of agouti-related protein (AGRP)/ Neuropeptide Y (NPY) neuron activity (53). Thus, FGF15/19 partially recapitulates the central action of leptin. Recent insights also suggest that hypothalamic FGF15/19 signaling can be antagonized by paracrine FGF produced within the hypothalamus (292). Moreover, acute FGF19 administration into the third-cerebral ventricle in rats reduces daily food intake and body weight, and acutely improves glucose tolerance (288). Conversely, administration of an FGFR1-3 antagonist increases food intake and impairs glucose tolerance (288). It involves transient sympatho-adrenal activation and a reduction of insulin secretion (293). Another role for central FGF19 has recently emerged in glucose counter-regulation. ICV injections of FGF19 reduce the neuroglucopenia-induced activation of the dorsal vagal complex neurons and the parasympathetic nerve, thus lowering glucagon secretion (55). On the other hand, silencing FGF15 expression in the dorsomedial hypothalamus increases neuroglucopenia-induced glucagon secretion (55).

A single, low-dose ICV injection of FGF19 improves glucose intolerance within 2 h in *ob/ob* mice, independently of changes in energy balance (294). This direct antidiabetic action is due to increased peripheral glycolysis, and is independent of changes in insulin secretion or insulin sensitivity (294). In the same way, acute ICV injections of FGF19 reduce plasma glucose, corticosterone and adrenocorticotropic hormone (ACTH), independently of any change in plasma insulin and glucagon, in an insulinopenic rat model of T1D (295). In this study, FGF19 suppresses hepatic glucose production by reducing hepatic acetyl CoA levels (295). Indeed, the glucose-lowering action of FGF19 is due to the suppression of the HPA axis (295). In line with the insulin-independent glucose lowering effect of FGF15/19 signaling, FGF15 KO mice show impaired glucose uptake from the circulation (48) and more elevated postprandial glycaemia compared to wild-type mice, without any change in insulin sensitivity or glucagon concentrations (262).

Pleiotropic functions of FGF15/FGF19 in animals and humans are illustrated in Figure 4.

6. FGF19 in human diseases

6.1. Obesity and diabetes

Obesity

Several studies report that basal circulating FGF19 levels are significantly lower in obese patients relative to non-obese controls, without any strong relation to glucose metabolism or insulin sensitivity (166, 296-298). This suggests that excessive weight in itself drives the decrease in FGF19 levels. In this way, FGF19 levels are mainly correlated to visceral adiposity (166, 299). Moreover, expression of KLB is significantly decreased in the visceral adipose tissue of obese patients, while it is increased in their liver (297). Nevertheless, 3 weeks to 6 months of lifestyle-induced weight loss does not consistently restore basal and postprandial circulating levels of FGF19 (296, 300, 301).

Type 2 Diabetes

Other studies report that basal circulating FGF19 levels are inversely correlated to glucose metabolism or insulin sensitivity. Notably, patients with metabolic syndrome or T2D have lower circulating FGF19 levels than healthy controls (73, 302, 303). Moreover, basal FGF19 levels are negatively associated with fasting glycaemia and independently associated with the deterioration of glucometabolic status (304). Patients with T2D have lower circulating FGF19 levels than nondiabetic patients, irrespective of body weight (163). Circulating levels of FGF19 are also significantly reduced in women with gestational diabetes mellitus relative to healthy pregnant women (305).

6.2. Liver and biliary diseases

NAFLD

Some studies report that patients with NAFLD present similar basal FGF19 levels to healthy subjects (306, 307). Nevertheless, their hepatic response to FGF19 is impaired when they present insulin resistance (306). Other studies show that FGF19 levels are significantly lower in patients with NAFLD than in controls (308, 309). This decrease could be related to reduced FGF19 production caused by a disproportionate increase in the amount of DCA at the expense of CDCA (a most potent FXR agonist) (309). In obese adolescents with NAFLD, FGF19 levels are dampened compared to controls, with an inverse correlation between FGF19, alanine aminotransferase (ALT), and triglycerides levels (310). In children with NAFLD, serum FGF19 are inversely associated with hepatic damage (311, 312). KLB expression decreases in children livers with increasing severity of NAFLD (311).

In a recent phase 2 clinical study, the reengineered FGF19 analogue NGM282 (also known as M70 in pre-clinical studies) produced a rapid and significant reduction in liver fat content in patients with NASH (313). In fact, after 12 weeks of treatment (3 or 6 mg SC) 85% of patients achieve a reduction of more than 30% in fat content, associated with significant reductions in both ALT and aspartate aminotransferase (AST) (313). Liver fat content is completely normalized in 26%-39% of patients (313).

Cirrhosis

FGF19 expression is increased in cholestatic non-cirrhotic and cirrhotic livers compared to control livers (64, 314). Both circulating and hepatic levels of FGF19 correlate with the severity of hepatic disease (314). Circulating FGF19 levels are higher in cirrhotic patients with primary biliary cirrhosis compared to non-cirrhotic patients with primary biliary cirrhosis or healthy individuals (315). FGF19 levels are strongly correlated with BA synthesis and the severity of

cholestasis (315). Administration of the FXR agonist obeticholic acid increases FGF19 levels in patients with primary biliary cirrhosis and improves markers of the disease, such as the alkaline phosphatase and total bilirubin levels (316). In patients with alcoholic hepatitis, circulating FGF19 levels are strongly increased and gene expression of FGF19 is induced in biliary epithelial cells and ductular cells (317). FGF19 levels correlate positively with total and conjugated BAs (in particular with conjugated CA), as well as with disease severity (317).

Cholelithiasis / Primary sclerosing cholangitis

The expression of FGF19 is reduced in ileal biopsies of gallstone carriers with normal weight (318), but circulating FGF19 levels are not related to the history of cholecystectomy (74). A marked elevation of circulating FGF19 levels is observed in patients with extrahepatic cholestasis caused by a pancreatic tumor (64). In patients with sclerosing cholangitis, basal FGF19 levels are unchanged (319). However these patients exhibit a prolonged FGF19 peak in the circulation following a CDCA oral challenge (319), and an increased FGF19 protein content in the ascending colon (320). UDCA withdrawal does not change circulating FGF19 levels in patients with primary sclerosing cholangitis (321).

6.3. Intestinal diseases

Patients with BAs malabsorption

BA malabsorption leads to excessive fecal BA excretion and diarrhea. It is also associated with lack of feedback regulation, resulting in additional BA production, saturating ileal transport. Circulating FGF19 levels are significantly lower in patients with BA malabsorption compared to controls (249, 322, 323), while a subgroup of hypertriglyceridemic patients presented higher values (324). Impairment in ileal FGF19 expression and responsiveness contributes to the multifactorial etiology of primary BA diarrhea (324-326). FGF19 represents both an opportunity for diagnosis and treatment of the pathophysiological defect. From a genetic point of view, a DIET1 coding variant which increases the amount of FGF19 secreted has a skewed prevalence between patients with BA diarrhea cases and controls (96), suggesting that genetic variation impacting FGF19 secretion also affect BA metabolism in pathological conditions (96).

Inflammatory bowel syndrome

Patients with inflammatory bowel syndrome (IBS) have similar FGF19 levels to controls (327, 328), but a subset of IBS patients with low BA turnover rate presents lower FGF19 levels (327). Variants in KLB and FGFR4 may identify subgroups of patients with IBS showing i) elevated serum C4 (329), ii) changes in BA/colonic transit (330, 331), or iii) a positive response to treatment with BA sequestrants (332). In pediatric onset of intestinal failure, total or partial loss of the ileum decreases circulating FGF19 levels (333, 334). In these patients, FGF19 levels negatively correlate with the extent of portal inflammation, serum TNF-α and hepatic fibrosis stage (333). Low FGF19 levels are also associated with liver injury featured by liver bile duct proliferation, inflammatory infiltration, predominance of primary BA, hepatocyte apoptosis and fibrosis (334). Reduced FGF19 levels are associated with ileal resection, diarrhea and Crohn's disease activity, suggesting a role of FGF19 as a biomarker for diseases affecting the ileum (250). FGF19 levels are decreased in patients with Crohn's disease when compared to healthy controls, or even when compared to patients with ulcerative colitis (335).

6.4. Renal diseases

Circulating FGF19 levels are increased during end-stage renal disease in patient undergoing chronic hemodialysis compared to normal subjects (336). The postprandial FGF19 response is

also blunted in patients with chronic kidney disease compared to control subjects, in association with impaired insulin and C-peptide signaling (337).

6.5. Cancer

HCC

The action of FGF19 on hepatocyte proliferation observed in mice and cell culture suggests a role in the occurrence or progression of HCC in humans. FGF19 and FGFR4 are co-expressed in primary human liver tumors (209). FGFR4 expression is elevated in liver tumors relative to normal tissues (210). FGF19 is equally significantly overexpressed in HCC compared to corresponding noncancerous liver tissue and is an independent negative prognostic factor for survival (52, 212, 213, 338). Expression of FGF19 is associated significantly with larger tumor size (338) and correlates with sensitivity of cells to FGFR4 inhibitors (339). Hepatic tissue protein content of FGF19 and FGFR4 significantly correlates with histopathologic changes from fatty liver to HCC (340). FGF19 levels are also significantly increased in the circulation of patients with HCC compared to controls (340) and are lowered after surgical tumor resection (212). A positive correlation is observed between the expression of FGF19 and the EGFR ligand amphiregulin (211), while FGF19 expression is negatively associated with the expression of E-cadherin in HCC tissues (213), thus highlighting a role in epithelial-mesenchymal transition. FGF19 expression is also correlated with the expression levels of STAT3 target genes in HCC tumors (52). High expression of FGF19 signaling actors and low expression of FGF19 signaling repressors correlate with the aggressiveness of hepatoblastoma tumors in children (216).

In addition to the overexpression of FGF19 in hepatic tumors, amplification of the FGF19 gene region is also observed in HCC, corroborating a role as a tumor-promoting gene (215). Genomic profiling of HCC at early stages reveals high-copy number amplifications of the gene region including the FGF19 gene in 5% of cases, in association with liver cirrhosis, especially in patients infected with hepatitis B (341). FGF19 amplification is also observed at advanced stages in aggressive HCC tumors (342). A gain in FGF19 copy number is detected more frequently among patients with a complete response to the multi-kinase inhibitor sorafenib compared to patients with incomplete response (343). Genetic alterations in FGFR4, including frequent polymorphisms, are also observed in HCC tissues compared to control tissue pairs (344). *In vitro* FGF19 stimulation confirmed a mechanistic link between FGFR4 activities and tumor aggressiveness in HCC cell lines (344). The inhibition of FGF19/FGFR4 signaling overcomes sorafenib resistance (345, 346). In a genome-wide mapping of DNA methylation, the FGF19 gene appears significantly hypermethylated in the tumor tissues compared to paired adjacent peritumoral tissues (347). Therapeutic approaches targeting FGFR4 in HCC, including ongoing clinical trials, have been previously reviewed (348).

Digestive tracts cancers

FGF19 is overexpressed in gastric cancer and is associated with depth of invasion and lymph node metastasis (349). *In vitro*, FGF19 enhances migration and the invasion abilities of gastric cancer cells (349).

FGF19 and FGFR4 are co-expressed in primary human colon tumors and in a subset of human colon cancer cell lines (209). In these cells, FGF19 increases tyrosine phosphorylation of beta-catenin, and inhibits beta-catenin/E-cadherin binding (350), suggesting that inactivation of FGF19/FGFR4 signaling could be a therapeutic target. FGF19 is required for PXR-induced cell growth, invasion, and metastasis in both human colonic tumor cell lines and mice xenografted

with tumor cells (351). PXR binds to the FGF19 promoter in human colon tumor cells as well as in normal intestinal crypt cells, but promoter activation occurs only in cancer cells (351).

The implication of FGF19 in pancreatic tumors and cholangiocarcinoma remains more elusive. FGFR4 expression is markedly increased in high-grade pancreatic ductal adenocarcinoma and pancreatic intraepithelial neoplasia compared to the normal pancreas (352). FGF19 seems to contribute to tumor suppression by increasing cellular adhesion to the extracellular matrix in pancreatic ductal adenocarcinoma cells (352). FGF19 expression is reduced in cholangiocarcinoma tumors compared to normal bile duct tissue (353). In intrahepatic cholangiocarcinoma, high expression of FGF19 is significantly associated with a better survival (354).

Reproductive tissues cancers

In addition to hepatic and gastrointestinal cancers, several studies have implicated FGF19 in cancers of reproductive tissues including the prostate, ovary and breast.

FGF19 is expressed in primary and metastatic prostate cancer tissues, where it functions as an autocrine growth factor (355). Exogenous FGF19 promotes growth, invasion, adhesion, and colony formation of prostate cancer cells (355). In contrast, FGF19 silencing in prostate cancer cells expressing autocrine FGF19 decreases invasion and proliferation *in vitro* and tumor growth *in vivo* (355). Moreover, higher levels of Prostate-Specific Antigen (PSA) are observed in patients with prostate tumors positive for FGF19 staining, and survival is higher in patients with FGF19-negative tumors (356). FGF19 enhances the viability and the expression of N-cadherin in human prostate adenocarcinoma cells while suppressing the expression of E-cadherin and caspase 3 (356).

High expression of FGF19 predicts unfavorable prognosis of advanced-stage serous ovarian cancer (357). *In vitro*, FGF19 promotes ovarian cancer cell proliferation and invasion by activating the FGFR4/Akt-MAPK signaling pathway (357).

FGF19 is also involved in breast cancer (358). FGFR4/FGF19 co-expression is observed in almost one third of primary breast tumors (359). A subset of basal-like, breast cancer cells secretes FGF19, and FGFR4 is a mediator of cell survival via activation of PI3K/Akt signaling (359). The Y367C missense mutation in FGFR4 in a human breast cancer cell line confers insensitivity to FGFR4 ligand stimulation, but elicits a constitutive phosphorylation leading to activation of the MAPK cascade driven tumor growth (360).

Other cancers

FGF19 expression is observed in the majority of malignant cells of patients with thyroid cancer (361). The amount of FGF19 protein in thyroid cancer tissues is significantly higher than in normal tissues (361). FGF19 overexpression is also significantly associated with advanced stages of the disease, including tumor node metastasis, extrathyroidal invasion, and distant metastasis (361). Amplification of the FGF19 genic region is observed in a subset of patients with advanced medullary thyroid carcinoma (362). Higher circulating levels of FGF19 are found in patients with papillary thyroid cancer, follicular thyroid cancer and anaplastic thyroid cancer when compared to patients with multinodular nontoxic goiter and healthy controls (363). FGF19 is equally highly expressed in mesenchymal stem cells-exosomes which accelerates nasopharyngeal carcinoma progression (364). FGF19 and FGFR4 are also co-expressed in primary human lung tumors (209). In patients with lung squamous cell carcinoma, amplification of the FGF19 genic region, as well as gene overexpression in the tumor compared to adjacent non-tumoral tissues is found more frequently with smoking (365, 366).

7. Conclusions and perspectives

Human FGF19 and its murine FGF15 homolog are fascinating hormones harboring a wide diversity of actions, from fetal morphogenesis to stimulation of adult tissues growth (liver, muscle), through control of BA synthesis and insulin-like postprandial activity. Moreover, administration of supraphysiological doses of FGF19 strikingly mimics the effects of FGF21, increasing energy expenditure and glucose utilization. These biological properties explain the strong scientific enthusiasm for these molecules and the optimism concerning their use as metabolic drugs.

Based on the evolutionary conservation of their surrounding genetic loci, FGF19 and FGF15 genes are considered as orthologs (21). However, their homology is weaker than all other human/mouse FGF family members (19), suggesting some divergence in terms of production and biological actions. FGF19 and FGF15 are both highly expressed in the ileum. In the liver, FGF15 is absent in mice (38, 56) but FGF19 is induced in humans under cholestatic conditions (63-65, 314, 315), raising questions about this tissular contribution. In addition, high levels of FGF19 are observed in human bile (67, 68) due to high production levels in gallbladder cholangiocytes and extrahepatic bile duct (20, 66). This suggests either an exocrine or a paracrine function (anti-inflammatory, secretagogue?), which remains to be elucidated. Molecular regulation of FGF19 and FGF15 also reveal some differences, in particular concerning the nuclear receptors involved. Furthermore, the role of gut microbiota in the regulation of FGF15/19 is not fully elucidated in mice and presently unknown in humans.

Beyond their regulation, FGF19 and FGF15 also present structural divergences. Of note, FGF15 contains a specific unpaired cysteine residue, which allows dimerization of FGF15 monomers (28). Thus, conformational divergence between FGF19 and FGF15 could induce differences in ligand-receptor affinity and explain functional disparities. The systemic effect of FGF15 has long been under-investigated due to the instability of the molecule (48, 69, 72). In contrast, human FGF19 has been intensively studied in mice, albeit with concerns about technical bias and limitations associated with the use of human FGF in murine models (expressing mouse FGFRs). Moreover, clinical studies, as well as human primary cultures reveal some differences from what is observed in mice, complicating the translation of mouse-derived knowledge to the human situation. The understanding of the role of FGF15/19 in metabolism is further complicated by the fact that beyond metabolic consequences directly resulting from FGFR signaling, FGF15/19 also modulates levels and composition of BAs, master regulators of energy expenditure, lipid and glucose metabolism. In fact, both FGF19 and FGF15 repress hepatic BA production and shift BA synthesis from the neutral to the alternative BA synthesis pathway. However, due to differences in BA metabolism among species, FGF15 action increases hydrophilicity of the BA pool in rodents, while FGF19 increases hydrophobicity of the BA pool in humans. This effect on BA composition also impacts differently FXR and TGR5 signaling in mice and humans and deserves further metabolic investigation. New animal models more closely mimicking human physiology in terms of BA biology, could provide functional and mechanistic insights that better delineate particular clinical situations. FGF19 appears more potent than FGF15 for correcting murine obesity (28). However, unlike FGF15, FGF19 induces hepatocyte proliferation and ultimately HCC in mice (28). This side effect has dampened the interest of several pharmaceutical companies for FGF19, leading them to focus on non-mitogenic FGF21 as a metabolic drug candidate. The action of FGF19 on hepatocyte proliferation is directly dependent on STAT3 activation and downstream target genes (28, 51, 52). Reengineering of FGF19 allows suppression of its ability to induce STAT3 phosphorylation and thus its

oncogenicity (50). Thus, genetically modified FGF19 (M70) retains biological properties and protects mice from cholestatic liver injury (50, 257, 258). From a translational point of view, this compound also reduces BA synthesis in humans (257) and is currently being tested in patients suffering from primary biliary cirrhosis and T2D (259). More recent studies demonstrate that M70 reduces hepatic fat content in patients with NASH in a phase 2 clinical trial (313), currently representing the most significant advance in the use of FGF19 as a drug.

FGF21 has grown in interest for treating obesity and T2D (17). Nevertheless, it is already upregulated during metabolic diseases, reflecting either a compensatory mechanism to limit metabolic insults or a state of FGF21 resistance. In contrast, FGF19 levels are decreased in human metabolic diseases, including obesity (166, 296-298), T2D (62, 73, 163, 302, 303) or NAFLD (308, 309). Even if these clinical studies are correlative in nature and do not provide mechanistic explanations, they support supplemental approaches to treat metabolic and hepatic diseases. Moreover, in addition to its FGF21-like glucose lowering activity, FGF19 could also be beneficial in diseases involving BA excess or gut-related FGF19 deficiency. On the other hand, FGF19 is overexpressed in HCC tumors compared to corresponding control hepatic tissue (52, 212, 213, 338). It suggests that inhibition/blockade of FGF19 signaling can also be beneficial in this pathological context in which novel therapeutic approaches are also urgently needed.

Abbreviations

AARE: amino-acid-response element; AAV: adeno-associated virus; ACTH: adrenocorticotropic hormone; AGRP: agouti-related protein; Akt: protein kinase B; ALT: alanine aminotransferase; ASBT: apical sodium-dependent BA transporter; AST: aspartate aminotransferase; ATF4: activating transcription factor 4; BA: bile acid; BAT: brown adipose tissues; C4: 7α-hydroxy-4-cholesten-3-one; CA: cholic acid; CCK: cholecystokinin; CDCA: chenodeoxycholic acid; CREB: cAMP regulatory element-binding protein; CYP7A1: cholesterol 7α-hydroxylase; CYP8B1: sterol 12α-hydroxylase; DCA: deoxycholic acid; DIO: diet-induced obesity; DSS: Dextran Sulfate Sodium; E: embryonic day; EGFR: epidermal growth factor receptor; eIF4B/E: eukaryotic translation initiation factor 4B/E; ER: Endoplasmic Reticulum; ERK1/2: extracellular signal-regulated kinase; FFA: free fatty acid; FGF: fibroblast growth factor; FGFR: fibroblast growth factor receptor; FOXC1: forkhead box C1; G-: glyco; FoxO1: Forkhead Box O1; FRS2α: FGFR substrate 2 alpha; FXR: farnesoid X receptor; GABA: gamma-aminobutyric acid; GSK: glycogen synthase kinase; HCC: hepatocellular carcinoma; HFD: high fat diet; HPA: hypothalamic-pituitary-adrenal; IBS: inflammatory bowel syndrome; IKKβ: inhibitor of NFκB; IL: interleukin; JNK: c-Jun N-terminal kinase; KLB: β-Klotho; KLF: Krüppel-like factor; KO: knock-out; LCA: lithocholic acid; MAPK: mitogen-activated protein kinase; MCA: muricholic acid; MDR2: canalicular phospholipid flippase; Mnk1: MAPK interacting protein kinases 1; mTOR: mammalian target of rapamycin; mTORC1: mammalian target of rapamycin complex 1; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; NPY: neuropeptide Y; Nrf2: nuclear factor erythroid 2 [NF-E2]-related factor 2; NTCP: sodium-taurocholate cotransporting polypeptide; OATP: organic anion-transporting polypeptide; Ost: organic solute transporter; PGC: PPAR-gamma coactivator; Pi: inorganic phosphate; PI3K: phosphoinositide 3-kinase; PKC: Protein Kinase C; PPAR: peroxisome proliferator-activated receptor; PSA: Prostate-Specific Antigen; PXR: pregnane X receptor; Ral: Ras-like; RAR: retinoic acid receptor; RYGB: roux-en-Y gastric bypass ; rpS6: ribosomal protein S6; RSK: p90RSK ribosomal S6 kinase; RXR: retinoid X receptor; S6K1: p70S6K ribosomal protein S6 kinase; SHP: small heterodimer partner; Shp2: non-receptor tyrosine phosphatase with two Src-homology 2 domains; siRNA: short interfering RNA; SISCAPA: isotope standards and capture by anti-peptide antibodies assay; SREBP: sterol regulatory element binding protein; STAT3: signal transducer and activator of transcription 3; T-: tauro; T2D: type 2 diabetes; TG: triglyceride; TGR5: (GPBAR1) BA

receptors; TNF-α: tumor necrosis factor alpha; UDCA: ursodeoxycholic acid; UGT: UDP-glucuronosyltransferase; VDR: vitamin D receptor; WAT: white adipose tissue.

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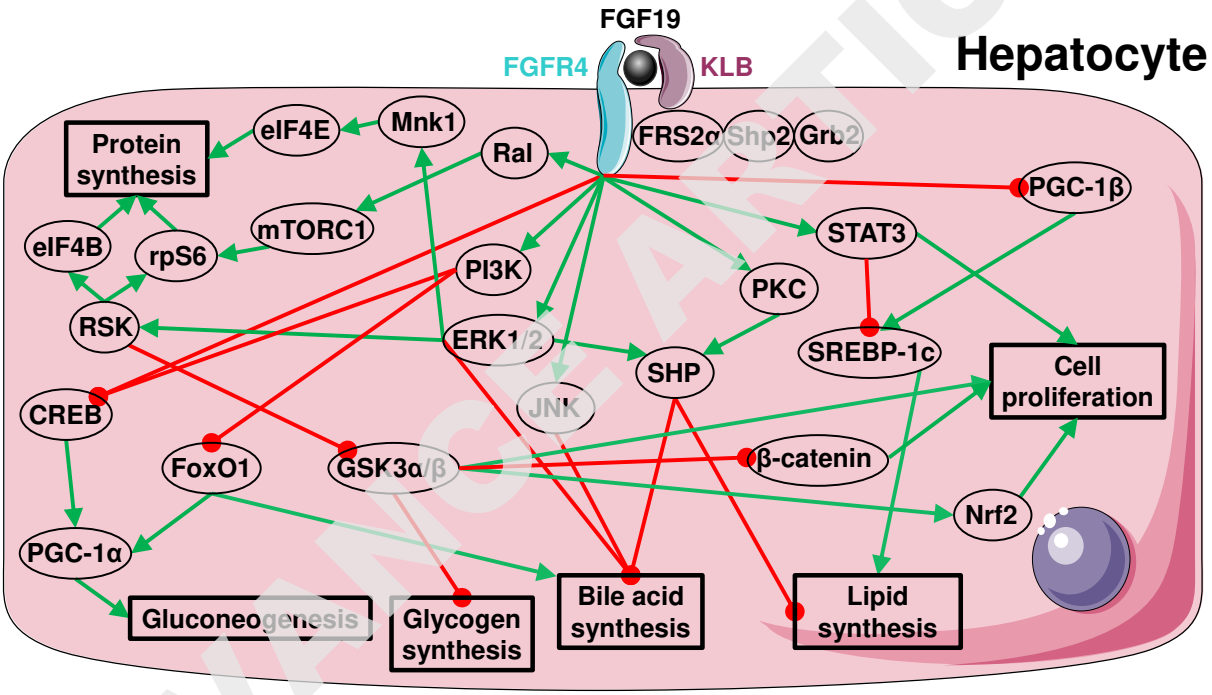
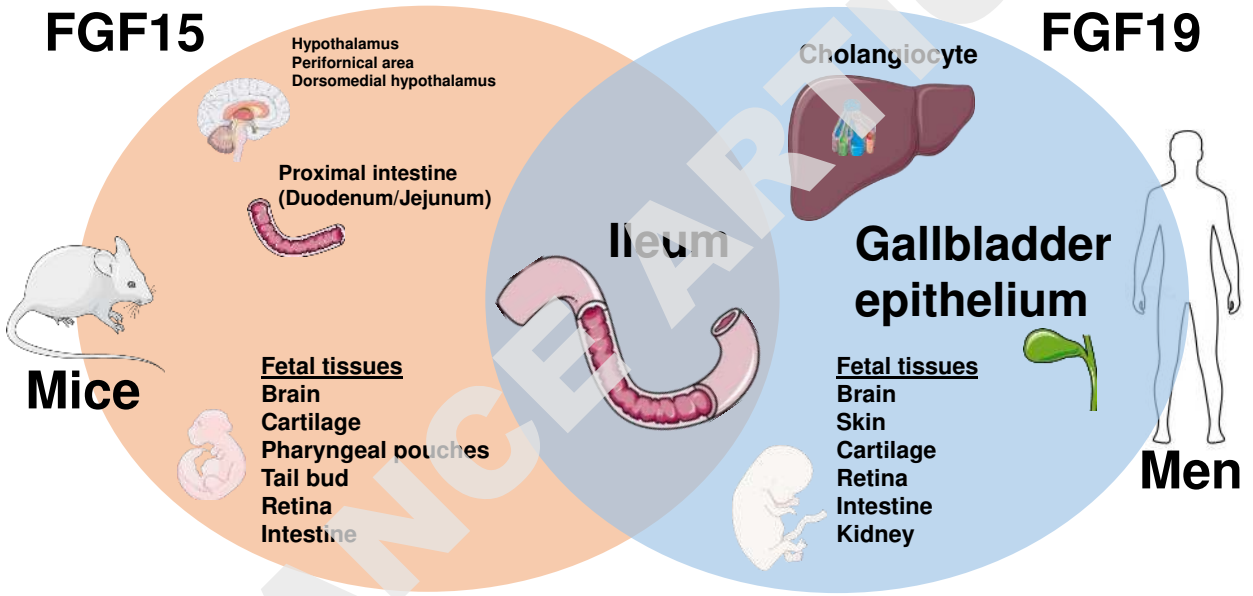
Figure 1: Intracellular signaling pathways triggered by FGF15/19 in the hepatocyte. FGF15/19 binds to tyrosine kinase receptor FGFR4 associated to the co-receptor β-Klotho (KLB). After recruitment of docking and adapter proteins, FGFR4 activation regulates the activity of several protein kinases and transcription factors involved in different biological processes. Green arrows represent activation/induction, red points represent inhibition/repression. Figure produced using illustrations from Servier Medical Art (smart.servier.com) under Creative Commons Attribution 3.0 unported license.

Figure 2: Comparison of main anatomical sites of FGF15 expression in mice and FGF19 expression in humans. Level of FGF15/19 expression is indicated by font/image size. Note that liver cholangiocyte FGF19 expression was found in humans with cholestatic conditions. Figure produced using illustrations from Servier Medical Art (smart.servier.com) under Creative Commons Attribution 3.0 unported license.

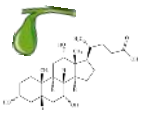
Figure 3: Regulation of FGF15/19 production in mice and humans. Stimulatory effects are indicated by plus signs (+), inhibitory effects by minus signs (−). Data are derived from clinical observations/studies and cell cultures in humans (h) and experimental studies and cell cultures in mice (m). Figure produced using illustrations from Servier Medical Art (smart.servier.com) under Creative Commons Attribution 3.0 unported license.

Figure 4: Pleiotropic functions of FGF15/19 in animals and humans. Stimulatory effects are indicated by plus signs (+), inhibitory effects by minus signs (−). Data are derived from clinical observations/studies and cell cultures in humans (h) and experimental studies and cell cultures in mice (m), rat (r), chicken (c) and zebrafish (z). Figure produced using illustrations from Servier Medical Art (smart.servier.com) under Creative Commons Attribution 3.0 unported license.





Nutrition
+ High-fat diet (m)
+ Carbohydrate (m, h)
+ Vitamin A (m, h)
+ Vitamin D (m)
- Pi (m)



Bile acids
+CA (m, h)
+ DCA (m, h)
+ CDCA (m, h)
+ LCA (m, h)
- T-βMCA (m)
- BA resins (m, h)

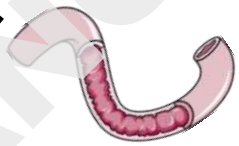
Chemical/drugs
+ GW4064 (m)
+ obeticholic acid (m, h)
- A4250 (ASBT inhibitor) (m, h)

Surgery
+ RYGB (h)
+ Sleeve gastrectomy (h)

Circadian rhythm
Max: end of dark phase (m)
Min: end of light phase (m)
Peaks 2 h after postprandial rise in BA (h)

Intestinal milieu
+ Microbiota (m)
- Antibiotics (m)

FGF15/19



Transcriptional regulators
+ FXR (m, h), PXR (h), VDR (m), RAR (h), ATF4 (h), Diet1 (m)
- SREBP-2 (h), KLF15 (m), GATA4 (m), miR-710 (m)