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Fibroblast Growth Factor 15/19 Expression, Regulation, and Function: An Overview

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Abstract

Since the discovery of fibroblast growth factor (FGF)-19 over 20 years ago, our understanding of the peptide and its role in human biology has moved forward significantly. A member of a superfamily of paracrine growth factors regulating embryonic development, FGF19 is unique in that it is a dietary-responsive endocrine hormone linked with bile acid homeostasis, glucose and lipid metabolism, energy expenditure, and protein synthesis during the fed to fasted state. FGF19 achieves this through targeting multiple tissues and signaling pathways within those tissues. The diverse functional capabilities of FGF19 is due to the unique structural characteristics of the protein and its receptor binding in various cell types. This review will cover the current literature on the protein FGF19, its target receptors, and the biological pathways they target through unique signaling cascades.

Keywords

Fibroblast growth factor 19; bile acid metabolism; carbohydrate metabolism; lipid metabolism; protein synthesis; farnesoid x receptor

1. Introduction

The fibroblast growth factor (FGF) family is comprised of 22 related proteins. Many members of the FGF family are involved in embryonic development. Thus, the discovery of FGF19 in the human fetal brain in 1999 conformed to the FGF family paradigm of embryonic growth factors (Nishimura, Utsunomiya, Hoshikawa et al., 1999). Further examination of embryonic tissues, mainly in chicken and zebrafish, identified FGF19 in the eye (Kurose, Bito, Adachi et al., 2004) and ear canal (Sanchez-Calderon, Francisco-Morcillo, Martin-Partido et al., 2007). Thus, during organogenesis, FGF19 has clearly

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defined roles in cellular growth and tissue development. However, in adult tissues, the expression of FGF19 becomes limited to the intestine (Milkiewicz, Klak, Kempinska-Podhorodecka et al., 2016), gall bladder (Zweers, Booij, Komuta et al., 2012), and liver (Milkiewicz et al., 2016,Wunsch, Milkiewicz, Wasik et al., 2015,Hasegawa, Kawai, Bessho et al., 2019,Johansson, Svensson, Almstrom et al., 2020). Unlike the paracrine or autocrine function of other FGF family members, in adult tissues, FGF19 functions as an endocrine factor, marking a unique change in functional activity. The functional purpose of FGF19 in adult tissues did not begin to be deciphered until 2002. FGF19 was identified as both a metabolic regulator (Tomlinson, Fu, John et al., 2002), and as an activator of hepatocellular carcinogenesis (Nicholes, Guillet, Tomlinson et al., 2002). Shortly thereafter, in 2003, FGF19 was found to regulate bile acid metabolism (Holt, Luo, Billin et al., 2003). However, it was not until 2011 that FGF19 was found to promote protein synthesis in the liver (Kir, Beddow, Samuel et al., 2011). A further role of FGF19 function to prevent muscle wasting and increase hypertrophy in skeletal muscle was discovered in 2017 (Benoit, Meugnier, Castelli et al., 2017). The diverse range of function of FGF19 is attributed to its unique structure compared to the other FGFs, and its affinity for binding to its cognate heterodimer surface receptors. The action of FGF19 on these receptors and the downstream pathways that are activated in a tissue-specific manner are still an active area of investigation. This review will focus on our current understanding of FGF19 as an endocrine factor involved in the currently known target pathways for bile acid homeostasis, glucose/lipid/energy metabolism, protein synthesis, and cancer development, as well as the role that FGF19 structure and interaction with its cognate receptors play in regulating these pathways.

2. Structure

There are 18 secreted protein members of the FGF family. The majority of the FGF members function in paracrine signaling and comprise FGF1 subfamily (FGF1 and FGF2), FGF4 subfamily (FGF4, FGF5, and FGF6), FGF7 subfamily (FGF7, FGF10, and FGF22), FGF8 subfamily (FGF8, FGF17, and FGF18), and FGF9 subfamily (FGF9, FGF16, and FGF20). The FGF19 subfamily consisting of FGF19, FGF21, and FGF23 is unique in that its members function as endocrine proteins. The family range in size from 150 to 300 amino acids in length. FGFs all have a conserved 120 amino acid region with highly variable N- and C-terminus regions. Within the conserved region, paracrine subfamily's structure is formed of 12 anti-parallel β-strands (β1 –β12) (Olsen, Garbi, Zampieri et al., 2003,Zhu, Komiya, Chirino et al., 1991). This conformation forms a β-trefoil fold consisting of three sets of four-stranded β sheets. Within the structure, there are heparin sulfate (HS) binding sequences that help the FGFs bind to their cognate receptors that also contain HS sequences. HS is a large oligosaccharide that is comprised of repeating GlcN(S)6O(S)-IdoA/GlcA(2S) disaccharide units. The endocrine members, FGF19, FGF21, and FGF23 are missing the β11 strand (Goetz, Beenken, Ibrahimi et al., 2007,Harmer, Pellegrini, Chirgadze et al., 2004). The resultant gap leads to the formation of an α-helical structure between strands β10 and β12. This extended loop displaces the HS region in FGF19, blocking the formation of hydrogen bonds at the N-sulfate and 2-O-sulfate groups present in HS (Goetz et al., 2007). Goetz et al. compared the crystal structure of FGF2 bound to HS and FGF19 which showed a four-amino acid region (Lys^{149}, Gln^{150}, Gln^{152}, and Arg^{157}) in FGF19 that could promote

FGF19 binding to HS (Goetz, Ohnishi, Kir et al., 2012). Deletion of Lys^{149}, led to complete loss of HS binding by FGF19, but did not alter FGF19's activation of signaling pathways or suppression of Cyp7a1 and Cyp8b1 gene expression. This decreased interaction with heparin sulfate allows for the FGF19 family of proteins to enter into circulation, rather than be bound by nearby receptors containing HS (Goetz et al., 2007).

3. Receptors

FGF19 enters circulation where it binds to a heterodimer receptor complex comprised of a Fibroblast Growth Factor Receptor (FGFR) and β-Klotho (KLB). The tissue specific expression of both receptors confer target specificity to the action of FGF19. This is unique to the FGF19 receptor subfamily, as the other FGFs bind to homodimer FGFRs in nearby cells where they are expressed (Romero-Fernandez, Borroto-Escuela, Tarakanov et al., 2011).

3.1 Fibroblast Growth Factor Receptors

There are four receptors in the FGFR family, FGFR1, FGFR2, FGFR3, and FGFR4. The FGFRs are relatively homologous with the sequence identity ranging from 53% – 70% (Gong, 2014). The common structural characteristics of the family include an N-terminal signaling sequence, three extracellular immunoglobulin (Ig) domains (IgI, IgII, and IgIII), an acid box region between IgI and IgII, a transmembrane domain, and an intracellular split tyrosine kinase sequence. The IgII and IgIII domains are responsible for ligand binding. Splice variants in the IgIII domain of FGFR1–3 lead to two variants for these receptors, labelled either "b" or "c" (Itoh and Ornitz, 2004). FGFR4 does not have this splice variant in the IgIII domain, so in total there are seven active receptors in the FGFR family: FGFR1b, FGFR1c, FGFR2b, FGFR2c, FGFR3b, FGFR3c, and FGFR4. The FGFRs display wide differential expression in tissues (Hughes, 1997). FGFR1 is expressed in adipose, brain, kidney, lung, heart, and skeletal muscle (Templeton and Hauschka, 1992). FGFR4 is abundantly expressed in liver, lung, gallbladder, and to a lesser extent in the small intestines, colon, pancreas, and adrenal gland (Lin, Wang, Blackmore et al., 2007). FGFR4 is unique to the other FGFRs in that FGF19, but not FGF21 nor FGF23, can bind to it. FGF21 and FGF23 can bind to the receptors FGFR1-FGFR3. FGF19 is able to bind to the "c" variants of FGFR1-FGFR3, but not to the "b" variants. The observed overlap in metabolic effects of FGF19 with FGF21 are due to the shared binding that these receptors have for FGFR1c (Kurosu, Choi, Ogawa et al., 2007,Perry, Lee, Ma et al., 2015,Lan, Morgan, Rahmouni et al., 2017). Whereas, the ability of FGF19 to regulate bile acids in the liver is directly related to FGFR4-FGF19 binding in hepatocytes (Wu, Coulter, Liddle et al., 2011).

3.2 β-Klotho

There are two members of the Klotho family, alpha- or beta-Klotho (KLA or KLB). These single-pass transmembrane proteins have an extracellular domain containing two tandem glycosidase-like domains, also referred to pseudoglcyoside hydrolases, designated KL1 and KL2 (Shiraki-Iida, Aizawa, Matsumura et al., 1998). Given the conformational difference in FGF19 that masks the heparin sulfate binding sequences, it has poor binding affinity to FGFR4. KLB functions to bring FGF19 and FGFRs in close proximity to one another, and

therefore increase binding affinity. The C-terminal tail of FGF19 binds to the single pass loop of KLB in two sites (Kuzina, Ung, Mohanty et al., 2019). Site 1 is a multi-turn D-P motif and site 2 is a S-P-S motif. Site 2 binding occurs at the pseudoglycoside hydrolase region in KL2. Modification on the FGF19 C-terminal domain to that of FGF21 causes a loss of binding to KLB (Wu, Lemon, Li et al., 2008). The IgIII domain of FGFRs bind to KLB (Lin et al., 2007,Wu, Ge, Gupte et al., 2007). KLB is only able to interact with the "c" isoforms of FGFR1–3, further limiting the target tissues that FGF19 can exert metabolic effects (Kurosu et al., 2007). For example, FGFR4 and KLB are only predominantly co-expressed in the liver (Lin et al., 2007,Fon Tacer, Bookout, Ding et al., 2010). It should be noted that there is differences in binding affinity for KLB and the FGFRs, with FGFR1c and FGFR4 having the greatest overall binding affinity for KLB (Kurosu et al., 2007). In humans, KLB expression is most abundant in adipose tissue, with moderate expression in liver and pancreas, and low expression in lung, bone, and skeletal muscle (Lin et al., 2007). It is not clear if FGF19 can bind to FGFRs without the presence of KLB in-vivo. In support of KLB dependence for binding of FGF19 to FGFRs, regulation of KLB expression can alter the efficacy of FGF19 signaling. Loss of hepatic KLB increases the bile acid pool and increases expression of genes associated with bile acid production (Katafuchi, Esterhazy, Lemoff et al., 2015). Additionally, KLB deficiency-mediated impairment of FGF19 signaling has been observed *in vivo*. In obese patients, KLB is repressed by micro-RNA 34a leading to impaired FGF19 response (Fu, Choi, Kim et al., 2012).

4. Rodent Orthologue FGF15

The mouse orthologue *Fgf15* was discovered in the embryonic mouse nervous system two years before human FGF19 was identified in brain tissue (McWhirter, Goulding, Weiner et al., 1997). The orthologues only share 51% sequence identity despite sharing similar functions (Nishimura et al., 1999). The expression pattern of FGF15 is well detailed through development. Northern blot analysis detected *Fgf15* mRNA appearance at day 11 in mouse embryos (McWhirter et al., 1997). Using in situ hybridization, *Fgf15* mRNA expression first appears on day 7.5 – 8 in the neuroectoderm. *Fgf15* mRNA displays highly dynamic expression within the central nervous system through gestational day 14. Like FGF19, once organogenesis is complete in the developing embryo, and tissues have reached maturity, the expression pattern of FGF15 shifts, with limited expression in the nervous system and very high expression in the intestine, predominantly in the ileum (Fon Tacer et al., 2010). It is important to note that FGF15 expression does not entirely match that of human FGF19 in mature tissues (Figure 1). Whereas both FGF15 and FGF19 are highly expressed in the ileum, FGF15 is not expressed in the gall bladder, bile ducts (cholangiocytes) or hepatocytes (Fon Tacer et al., 2010,Choi, Moschetta, Bookout et al., 2006). However, the expression pattern of FGFRs and KLB overlap considerably between mouse and human. FGFR1c in the mouse is broadly expressed including the adipose, brain, kidney, lung, heart, and skeletal muscle. FGFR4 is more restricted with high expression in liver, adrenal gland, and kidney, and low expression in intestine, gall bladder, and lung. KLB has the most restricted expression pattern with high abundance in adipose tissue and liver and lesser abundance in

the gall bladder, ileum, heart, brain, and skeletal muscle (Fon Tacer et al., 2010,Yang, Jin, Li et al., 2012).

The differences between FGF15 and FGF19 are not limited to expression pattern, as the binding activity of FGF15 to the cognate receptors FGFR/KLB differ as well. FGF15 can bind with FGFR4 in the liver, in a similar manner as FGF19. Unlike FGF19 that binds to FGFR1c with high affinity, FGF15 binding is weaker (Yang et al., 2012,Zhou, Luo, Chen et al., 2017). Detailed examination of the amino acid sequence of FGF15 identified a single unpaired cysteine (Cys-135) present in the β8-β9 loop region. This unpaired cysteine can lead to dimerization of two FGF15 proteins altering the ability of the peptide to efficiently bind FGFRs (Zhou et al., 2017,Williams, Harper Calderon, E et al., 2021).

The functional relevance of FGF15 and FGF19 binding differences cannot be understated. FGF15 is unable to bind to and activate human FGFR4/KLB, but human FGF19 can bind to and activate mouse FGFR4/KLB and FGFR1c/KLB (Ellis, Naugler, Parini et al., 2013). Further, more recent research on the binding efficiency of FGF19 to FGFR4 uncovered small point mutations that can decrease the binding affinity for FGF19 and FGFR4/KLB reducing the magnitude of downstream signaling pathway activation (Niu, Zhao, Wu et al., 2020). Thus, even small changes in the structure of FGF19 markedly change the response to target receptor. The dimerization of FGF15 likely reduces the diversity of tissue targets compared to FGF19, conferring different overall biological effects. In total, these observations raise important questions about the endogenous function of mouse FGF15 relative to human FGF19.

The role of FGF15 appears to be mainly limited to the functions within the liver achieved through intestinal-derived FGF15 binding to FGFR4/KLB. FGF15 has limited ability, relative to human FGF19, to activate signaling in peripheral tissues through FGFR1c/KLB binding. This paradigm is especially important when using the mouse to model disease states that involve alterations in FGF19 signaling. For example, in human cholestatic liver disease, FGF19 expression is induced in hepatocytes (Milkiewicz et al., 2016,Wunsch et al., 2015,Hasegawa et al., 2019,Johansson et al., 2020), but the functional relevance of hepatic FGF19 expression during cholestasis is unknown. Trying to model this in mice presents a considerable challenge, as even administration of FGF15 agonists to mice does not induce FGF15 expression in the liver (Inagaki, Choi, Moschetta et al., 2005). Similar consideration should be taken to interpreting the effects of activating FGFR1c/KLB in peripheral tissues in mice. As FGF15 does not appear to be regulating peripheral tissues via these pathways, the overlap to human response of FGF19 should be taken with caution. Use of other animal models that more closely model human FGF19 signaling would add more clarity on the role of FGF19 in species where FGF19 endogenously targets FGFR4 and FGFR1c target tissues. Other animal models express FGF19 similar to humans, such as pig (Call, Molina, Stoll et al., 2020,Vonderohe, Guthrie, Stoll et al., 2021,Gavalda-Navarro, Pastor, Mereu et al., 2018) and rabbit (Shang, Guo, Honda et al., 2013). Further research is needed to investigate the function of FGF19 in these species and whether they activate signaling pathways in multiple tissues via FGFR4 or FGFR1c receptors.

5. Transcriptional Regulation of FGF15/19 Expression

5.1 Transcriptional Activators

FGF15/19 is an inducible protein that has multiple sites within its promoter region for activation of its expression. The best-described transcriptional activators of FGF15/19 are members of the nuclear hormone receptor family of transcription factors. The bile acid responsive nuclear hormone receptor, farnesoid x receptor (FXR) is most closely associated with the role of FGF15/19 in regulation of bile acid homeostasis. FXR is highly responsive to primary bile acids and induces FGF19 in a dose-dependent manner when the bile acid chenodeoxycholic acid (CDCA) is administered in both humans and mice (Holt et al., 2003,Li, Pircher, Schulman et al., 2005). Within the *FGF19* gene, there are FXR-responsive binding elements (FXRE) in three promoter positions within 2000 kb upstream of the transcription start site (Miyata, Hata, Yamakawa et al., 2012) and within the second intron (Holt et al., 2003). The mouse *Fgf15* gene also contains a FXRE in the second intron of the gene, mirroring human *FGF19* (Li et al., 2005). In addition to FXR, the xenobiotic sensing nuclear hormone receptor pregnane x receptor (PXR) is also responsive to high concentrations of the toxic secondary bile acid, lithocholic acid (LCA), a derivative of CDCA (Kliewer and Willson, 2002). A PXR binding site was identified in the promoter region of *FGF19* within 300 bp of the transcription start site (Wistuba, Gnewuch, Liebisch et al., 2007). The mouse *Fgf15* gene does contain a homologous region within the promoter, but mouse and human activation of PXR differ in the downstream regulation of FGF19. FGF19 is potently induced in human intestinal cell culture by LCA or rifampicin treatment (Wistuba et al., 2007) and in piglets administered intravenous rifampicin (Guthrie, Stoll, Chacko et al., 2020); yet in mice, suppression of PXR increases the expression of FGF15 (Zhao, Xu, Shi et al., 2017).

In vitro models of stress have identified non-bile acid related transcriptional regulation of FGF15/19. In response to endoplasmic reticulum stress, the transcription factor activating transcription factor 4 (ATF4) can upregulate FGF19 expression by binding to the amino acid response element (AARE) (Shimizu, Li, Maruyama et al., 2013). *In vitro* culture of colonic myofibroblasts treated with carbon monoxide show a robust increase in FGF15 expression (Uchiyama, Naito, Takagi et al., 2010). A micro RNA targeted to *Fgf15* mRNA, miR-710, was significantly reduced during the treatment, suggesting that FGF15 post-transcriptional regulation is mediated by micro RNAs and can be transiently altered in response to cellular environmental changes.

5.2 Transcriptional Repressors

The transcriptional repression of FGF15/19 occurs through both direct binding and indirect suppression of transcriptional activators. The sterol regulatory element-binding protein 2 (SREBP2) is activated when cholesterol levels are low to upregulate genes in cholesterol biogenesis (Brown and Goldstein, 1997). In the human intestinal cell line LS174T, activation of SREBP2 reduced the expression of FGF19 (Miyata, Hata, Yamazoe et al., 2014). Subsequent analysis confirmed this repression was due to SREBP2 directly interacting with FXR, preventing binding to the *FGF19* promoter. This inhibition of FGF19 is somewhat paradoxical in response to low cholesterol levels. As FGF19 decreases the production of

bile acids, it spares cholesterol which is the precursor for bile acid synthesis. Therefore suppression of FGF19 by SREBP2 would increase the loss of cholesterol through elevated bile acid metabolism. Given this, whether the mechanism has any physiological relevance *in vivo* still requires further research.

Other direct mediators of transcriptional repression of the *Fgf15* promoter have been identified in mice and not yet confirmed in humans. Mice that have the intestinal deletion of Kruppel-like factor 15 (*Klf15*$^{-/-}$), but not liver deletion of *Klf15* have decreased bile acid concentrations, which is a key pathway FGF15 targets (Han, Zhang, Jain et al., 2015). Furthermore, in intestinal *Klf15*$^{-/-}$ mice, the circadian patterning of bile acid synthesis is lost, suggesting that KLF15 is the direct regulator of bile acid cycling. Exploration of the mouse *Fgf15* promoter region via chromatin immunoprecipitation assays confirmed that there are at least three promoter regions in the mouse *Fgf15* gene that are bound by KLF15. In additional support of the KLF15/FGF15 axis, studies examining the bile acid increasing effects of the type 2 diabetes drug, Teneliglipitn, found KLF15 activated through phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway and downstream suppression of FGF15 (Wang, Wu, Cui et al., 2020). In the intestine, the segmental expression of FGF15 along the intestine is also regulated by direct transcriptional repression. GATA binding protein 4 (GATA4) is highly expressed in the jejunum and has lower expression in the ileum. Mice with ileal knock-in *Gata4* have decreased expression of FGF15 and mice with jejunal knock out *Gata4* have increased FGF15 (Thompson, Wojta, Pulakanti et al., 2017).

In addition to direct suppression, there is indication that indirect suppression of FGF15 is possible. Treatment of mice with the glucocorticoid receptor (GR) agonist, dexamethasone, reduces the expression of ileal *Fgf15* mRNA, along with other FXR target genes (Jia, Zhang, Jia et al., 2019). GR was also capable of upregulating the PXR target gene, *Cyp3a11*, but treatment with PXR agonist, pregnenolone−16−α−carbonitrile, had no effect of *Fgf15* mRNA. The exact mechanism that drives *Fgf15* mRNA suppression is not clear. Also, whether this effect is recapitulated on human FGF19 has yet to be established.

6. Functions

6.1 Regulation of Bile Acid Homeostasis

FGF15/19 activation is associated with negative feedback regulation of bile acid synthesis. There are multiple key targets of FGF15/19-mediated regulation in the bile acids synthesis pathway, so a brief overview of the main aspects of bile acid synthesis will be highlighted. Bile acids are amphipathic molecules synthesized by hepatocytes in the liver to facilitate the absorption of dietary lipid. In humans, the primary bile acids are CDCA and cholic acid (CA). The synthesis of these two bile acids occurs via two pathways, the classical (neutral) and alternative (acidic). The neutral pathway is the predominant synthesis pathway in adults and results in the formation of both CA and CDCA (Pullinger, Eng, Salen et al., 2002). The enzyme, cytochrome P450 7A1 (CYP7A1), is the key synthetic enzyme in the neutral pathway for the initiation of bile acid synthesis. CA is formed by an additional modification via CYP8B1. Both CA and CDCA undergo side chain oxidation via the mitochondrial enzyme CYP27A1. Following this, peroxisomal carbon chain cleavage finalizes formation

of CA and CDCA. The acidic pathway is initialized by mitochondrial CYP27A1, rather than by CYP7A1. Unlike the neutral pathway, the acidic pathway can be initiated in multiple cell types, including cholangiocytes and macrophages. Several initial oxysterol intermediates are formed via CYP27A1 including 25-hydroxycholesterol and 26-hydroxycholesterol, which are themselves key regulators of cholesterol homeostasis (Cali and Russell, 1991,Li, Pandak, Erickson et al., 2007). The oxysterols formed in the acidic pathway need to be transported to hepatocytes for final processing to form bile acids. However, the acidic pathway can only lead to the synthesis of CDCA. In mice, there is synthesis of CDCA, but rather small amounts of the bile acid in circulation because CDCA is converted to α-muricholic acid (α-MCA) then modified to form β-MCA (Botham and Boyd, 1983).

Originally, α-MCA synthesis was believed to occur through Cyp3a11 (Cuesta de Juan, Monte, Macias et al., 2007), however newer research suggest that Cyp2c70 catalyzes α-MCA formation (Takahashi, Fukami, Masuo et al., 2016). α-MCA is then predominantly converted to β-MCA via C7 epimerization. Other species have a similar modification step following synthesis of CDCA. The pig converts CDCA to γ-muricholic acid, otherwise called hyocholic acid (HCA), via CYP4a21 (Haslewood, 1954,Lundell, Hansson and Wikvall, 2001). β-MCA and HCA are more hydrophilic than CDCA and far less cytotoxic, so species other than humans have an additional mechanism to protect the liver from high bile acid concentrations. After synthesis, bile acids are conjugated with either glycine or taurine in a two-step process of activation by bile acid:CoA synthase enzymes and amidation by bile acid:amino acid transferase enzymes. These bile acids are then transported via the bile salt efflux pump (BSEP) located in the canalicular membrane of hepatocytes to the gall bladder and intestines.

Bile acids that are in the small and large intestine can undergo additional modifications. Multiple species of bacteria, including *Lactobacillus (Elkins, Moser and Savage, 2001)*, *Enteroccocus (Wijaya, Hermann, Abriouel et al., 2004)*, *Bifidobacterium (Grill, Schneider, Crociani et al., 1995)*, and others (Rossocha, Schultz-Heienbrok, von Moeller et al., 2005) can deconjugate bile acids using bile salt hydrolase enzymes. Once deconjugated, a much smaller set of bacteria, some belonging to the genus Clostridium (Wells, Williams, Whitehead et al., 2003), have 7α/β hydroxylase enzymes that convert primary bile acids to secondary bile acids. CDCA is converted to LCA and CA is converted to deoxycholic acid (DCA). The secondary bile acids are much more hydrophobic than primary bile acids and more toxic to the liver (Heuman, 1989). Little LCA is reabsorbed, but the LCA that is gets rapidly re-amidated and sulfonated (Hofmann, 2004). Sulfonated LCA is unable to be reabsorbed once recirculated into the intestines. CDCA, CA, and DCA are reabsorbed in the intestines and recirculated to the liver resulting in approximately 95% of all bile acids recovered in the liver.

The process by which bile acids are synthesized is tightly regulated given the potential for cytotoxicity of high bile acid concentration and the large volume of bile acids that are recirculated back to the liver. Regulation of bile acid synthesis is predominantly focused on the action of CYP7A1. Prior to the identification of FGF19, FXR downregulation of CYP7A1 was thought to be primarily dependent on hepatic FXR-mediated upregulation of the small heterodimeric partner (SHP) (Goodwin, Jones, Price et al., 2000). SHP can bind

to transcription factors that activate CYP7A1 expression, including liver receptor homolog 1 (LRH-1, Nr5a2) and hepatocyte nuclear factor 4 alpha (HNF4), and block their promotion of *CYP7A1* mRNA transcription (Inoue, Yu, Yim et al., 2006,Lu, Makishima, Repa et al., 2000). However, studies in hepatic $Shp^{-/-}$ mice did not observe large increases in bile acid production suggesting there are SHP-independent mechanisms (Inagaki et al., 2005,Wang, Han, Kim et al., 2003). Early studies examining deletion of *Fgf15* in mice observed an impaired ability of mice to suppress CYP7A1 and an elevation in bile acid concentration, pointing to FGF15 as a clear mediator of bile acid regulation (Inagaki et al., 2005). Primary bile acids (predominantly CDCA) in the intestine bind to FXR leading to transcriptional upregulation of FGF15/19. After FGF15/19 is translated, it associates with the protein, DIET1; however, the exact function of DIET1 is not clear. The absence of DIET1 expression results in a decrease in circulating FGF15/19 (Lee, Ong, Vergnes et al., 2018,Vergnes, Lee, Chin et al., 2013).

Once secreted from the intestine, FGF15/19 circulates to the liver to repress bile acid synthesis (**Figure** 2). The non-receptor tyrosine phosphatase SHP2 complexes with and increases tyrosine phosphorylation of FGFR substrate 2 alpha (FRS2α) to initiate further downstream phosphorylation events (Li, Hsu, Li et al., 2014). In part, SHP2 may also act as a feed forward messenger as it leads to increased tyrosine phosphorylation of FGFR4, which presumably increases FGFR4 signaling activity. The downstream target of FRS2α and SHP2 is the non-receptor tyrosine kinase SRC, which is phosphorylated at amino acid position Tyr^{278} (Byun, Kim, Ryerson et al., 2018). SRC is responsible for activating the nuclear translocation of FXR via phosphorylation of FXR at Tyr^{67}. FXR translocation allows for activation of bile acid homeostasis genes including hepatic bile export transport genes, BSEP, organic anion solute transporter alpha/beta (OSTα/β), and multidrug resistance protein 2 (MRP2). SRC is also capable of phosphorylating mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 (MAPK/ERK1/2) the canonical pathway associated with CYP7A1 downregulation (Lin et al., 2007,Kurosu et al., 2007,Wu et al., 2007,Song, Li, Owsley et al., 2009). However, SRC knockdown of mouse primary hepatocytes only leads to a marginal decrease in ERK1/2 phosphorylation, so there is likely an additional direct action of FSR2α/SHP2 on ERK1/2 phosphorylation (Byun et al., 2018).

The mechanism by which ERK1/2 phosphorylation leads to CYP7A1 suppression is only partially understood. ERK1/2 phosphorylation of SHP at Ser^{2} may improve protein stability of SHP (Miao, Xiao, Kanamaluru et al., 2009). SHP is post-translationally regulated via ubiquitination at Lys^{122}/Lys^{123} which leads to its degradation. The ERK-mediated phosphorylation of SHP blocks ubiquitination, increasing the protein abundance of SHP. More recently, the transcription factor EB (TFEB) was identified as a positive regulator of CYP7A1 expression that could be suppressed through ERK1/2 (Wang, Gunewardena, Li et al., 2020). During cholesterol induced lysosomal stress, TFEB translocates to the nucleus and binds to the *CYP7A1* promoter upregulating gene expression. In doing so, TFEB reduces cholesterol through enhanced bile acid synthesis. In the liver cell line, HepG2, inhibition of ERK1/2 increases TFEB-targeted upregulation of CYP7A1. Conversely, FGF19-mediated activation of ERK1/2 decreases nuclear translocation of TFEB. Further analysis of TFEB identified a single serine residue, Ser^{211} that ERK1/2 targets to prevent

nuclear translocation of TFEB. (Wang et al., 2020). A second downstream target of the FGF19 signaling pathway in the liver, mammalian target of rapamycin (mTOR), is also capable of phosphorylating TFEB on Ser^{211} and preventing nuclear translocation (Wang et al., 2020,Wan, Tian, Tan et al., 2016). Despite ERK1/2 being upstream of mTOR in the FGF19 signaling pathway, inhibitor studies strongly indicate that either ERK1/2 directly or mTOR can prevent TFEB translocation, leading to suppression of CYP7A1 expression.

The role of the acidic pathway for bile acid synthesis in adults is typically considered minor. However, infants have high placental transfer and urinary output of metabolites specific to the acidic pathway, suggesting it supplies a greater contribution to their bile acid pool (Tohma, 1996,Tazawa, Yamada, Nakagawa et al., 1984). In adults, there is indication that the acidic pathway has an important role in bile acid synthesis during primary biliary cirrhosis (PBC), wherein CYP7A1 is repressed, but bile acid synthesis is still active (Wunsch et al., 2015). Hepatic FGF19 is significantly increased in PBC patients, and is potentially the source of CYP7A1 repression. However, given continued bile acid synthesis, this would suggest that FGF19 is not able to suppress bile acid synthesis in the acidic pathway in hepatocytes. Since the acidic pathway is not limited to hepatocytes, other cells in the liver, such as cholangiocytes, could supply a source of oxysterols for conversion to bile acids. In cholangiocytes, cholesterol can be converted to oxysterols via the acidic pathway, which can then be transported back to the hepatocyte via the peribiliary plexus to undergo further conversion to bile acids (Xia, Francis, Glaser et al., 2006). In hepatocytes, there does not appear to be a direct regulatory effect of FGF19 on CYP27A1 synthesis of oxysterols in the acidic pathway. However, in cholangiocytes, FGF19 induces a p38-dependent signaling pathway that decreases the expression of CYP27A1 (Jung, York, Wang et al., 2014). This reduction can decrease oxysterol production in cholangiocytes. Whether reduction in the oxysterol production equates to reduced bile acid synthesis from the acidic pathway is not known. It may be that the oxysterols production is locally used to regulate cholesterol metabolism, rather than use for precursors to bile acid synthesis. Yet, this presents and intriguing potential bile acid synthesis mechanism in cholangiocytes that warrants further investigation.

Bile acids upregulate expression of FGF19 in the intestine by binding to the FXR. However, FXR is not the only bile acid responsive receptor in the body. In the intestine and macrophages, G-protein-coupled bile acid receptor (TGR5) is bound by DCA. TGR5 is a key regulator of metabolism that promotes improved glucose control and reduced obesity, thus many metabolic targets of TGR5 overlap with FGF19 (Guo, Chen and Wang, 2016). In the liver, sphingosine 1 phosphate receptor 2 (S1PR2) can activate hepatic Akt and ERK pathways to enhance glucose metabolism, regulate bile acid synthesis, and lipogenesis (Studer, Zhou, Zhao et al., 2012), as well as, enhance liver regeneration (Ikeda, Watanabe, Ishii et al., 2009). Like FXR and TGR5, S1PR2 also binds to bile acids for activation, with taurine conjugated CA being the most potent ligand. Because FGF15/19 can suppress bile acid synthesis, it can alter the production of specific bile acids and indirectly effect metabolism through suppression or generation of bile acids that target TGR5 and S1PR2. In mice, infusion of FGF19 decreases taurine conjugated CA (Wu et al., 2011). This change represents a shift from the neutral pathway to the acidic pathway following suppression on CYP7A1. *FGFR4*$^{-/-}$ mice conversely have markedly increased concentration of taurine

conjugated CA, the ligand for S1PR2. FGF15/19 in this way act as a suppressor of the S1PR2 pathway. Anti-FGF19 antibody treatment in Cynomolgus monkeys causes a large increase in bile acid production, which results in much greater concentration of bile acids in the intestines (Pai, French, Ma et al., 2012). This resultant increased bile acid substrate for bacteria increases the presence of secondary bile acids produced in the gut, including the TGR5 target DCA. Therefore, when FGF19 is active, it may suppress other pathways that contribute to metabolic regulation through indirect methods by reducing the production of bile acid that target them.

FGF15/19 can also impact the flow of bile by mediating gall bladder filling (Choi et al., 2006). *Fgf15*$^{-/-}$ mice have no bile in their gall bladders after fasting. Administration of either FGF15 or FGF19 causes significant gall bladder filling. In these mice, after cannulation of the common hepatic duct, there was no observed increase in bile flow from the liver, suggesting that filling of the gall bladder is independent of increased outflow of bile from the liver. Whether the target of FGF15/19 is the cholangiocytes or smooth muscle has not been established, nor is the receptor target for gall bladder filling entirely clear. In mice, there is a >10-fold greater expression of FGFR3 compared to FGFR1, FGFR2, and FGFR4. Given this, it has been suggested that FGFR3 may be the primary target for FGF15/19 in the gall bladder. However, in human cholangiocytes, there is abundant expression of FGFR4 (Zweers et al., 2012). In mice, it is likely that FGFR4 is still the primary FGFR involved in gall bladder filling. In part, this would be due to the ability of FGF15 to form dimers, so it is not as potent a ligand for FGFR3c, as FGF19 (Zhou et al., 2017). This is also partially supported in *Fgfr4*$^{-/-}$ mice, which have gall bladders markedly decreased in size, suggesting that they do not undergo much filling (Yu, Wang, Kan et al., 2000). However, *Fgfr4*$^{-/-}$ mice can restore gall bladder filling with FGF19 administration (Choi et al., 2006). This finding may suggest that some effects on gall bladder filling are from local binding to FGFR3 in the gall bladder, or activation of sympathetic nervous system signals through FGFR1c, but this has not been established experimentally. In humans, it is also likely that FGFR4 is the main target given the high expression in gall bladder, but may be possible that FGFR3 or other FGFRs have functional activity as well. The action of FGF19 on the gall bladder is mediated, at least in part, through a c-AMP dependent relaxation of smooth muscle within the gall bladder (Choi et al., 2006). It is also capable of preventing cholecystokinin-mediated contraction of gall bladder smooth muscle.

The gall bladder is also a large producer of FGF19 in humans, but mice do not produce any FGF15 in their gall bladders (Zweers et al., 2012,Barrera, Azocar, Molina et al., 2015). The exact purpose of the large quantity of FGF19 in gall bladder is not entirely clear. Though it has been postulated it may have protective effects against bile acid toxicity, there have been no studies to directly support this, or to give insight into how FGF19 could protect from bile acid toxicity. In patients that have undergone cholecystectomy, there is increased synthesis of bile acids and altered diurnal rhythm of FGF19. However, they have no changes in serum bile acid concentration or cholesterol concentration (Barrera et al., 2015). Moreover, in cholecystectomy patients treatment with OCA markedly increased the FGF19 concentration in bile and risk for gallstones (Al-Dury, Wahlstrom, Panzitt et al., 2019).

6.2 Regulation of Glucose and Lipid Metabolism

FGF15/19 displays biphasic fluctuations regulated in part by feeding/fasting patterns of dietary intake. In response to a meal, FGF19 increases transiently for approximately 3 hr and decreases over time during fasting (Lundasen, Galman, Angelin et al., 2006). Thus, the discovery of FGF15/19 as a regulator of metabolism fits with other classic hormones such as insulin and glucagon that also have altered expression patterns in response to dietary intake. Unlike the role of FGF15/19 in regulation of bile acid synthesis, the actions of FGF15/19 on energy expenditure, glucose metabolism, and lipid metabolism are more heterogeneous. Therefore, it is important to delineate the role of FGF15 and FGF19 in the context of metabolism before going into detail on specific activities in various organs. In the liver, FGF15 and FGF19 bind to FGFR4/KLB, and have many shared downstream effects specific to actions in the liver, hence the similar bile acid responses. However, in extrahepatic tissues, the primary targets of FGF15/19 are FGFR1c-3c. Since FGF15 has much lower affinity for FGFR1c-3c compared to FGF19 there is likely a large species divergence in observed metabolic effects, with a much greater effect from FGF19. The literature can be more complicated when examining mouse studies that use endogenous FGF15 response in mice compared to studies that use FGF19. Given this, much of the reviewed literature on metabolism will focus on the role of FGF19 in modulating metabolism, rather than the specific role of FGF15.

6.2.1 Glucose Metabolism—The regulation of glucose in the body is a sophisticated interplay between glucose production (gluconeogenesis), glucose uptake (both peripheral and hepatic), and glucose storage (glycogen synthesis). FGF15/19 exerts regulatory pressure at all three of these key pathways to modify whole body glucose concentrations. As mentioned above, FGF19 likely exerts more global glucose control than FGF15, given extrahepatic targeting, which will be discussed in detail.

Unlike bile acid regulation, which is entirely dependent on FGF15/19 binding to FGFR4/KLB in the liver, control over glucose homeostasis occurs through both hepatic FGF15/19 binding to FGFR4/KLB and extrahepatic tissues activated by FGF19 binding to FGFR1c/KLB (Figure 3). When observing whole body glycemic control, FGF19 is capable of reducing glucose levels in obese models of mice. In high fat diet fed obese mice, transgenic overexpression of FGF19 imparts resistance to post-prandial hyperglycemia, increases sensitivity to insulin, and lowers circulating insulin levels (Tomlinson et al., 2002). Likewise, in *ob/ob* leptin deficient obese mice, transgenic overexpression of FGF19 improves fasting blood glucose and glucose excursion after glucose tolerance tests (Fu, John, Adams et al., 2004). The injection of FGF19 into *ob/ob* mice has a similar effect with reduced post-prandial glucose levels and improved glycemic response following glucose tolerance test (Fu et al., 2004,Wu, Ge, Baribault et al., 2013). FGF15 does not confer the same protective effects against hyperglycemia, as does FGF19. In *db/db* diabetic mice and diet induced obesity mice, adeno-associated virus (AAV) injections of FGF15 failed to lower glucose levels, whereas AAV-FGF19 administration restored blood glucose concentrations to that of healthy control mice (Zhou et al., 2017). This difference highlights that uptake of glucose in peripheral tissues, at least in mice, through FGFR1c/FGF19 is important for whole body glucose uptake. In the liver, the primary mechanism through

which FGF15/19 is able to reduce circulating glucose levels and enhance the activity of insulin is through increasing glycogen synthesis and suppressing gluconeogenesis. In fasted mice, administration of FGF19 enhances glycogen synthesis through activation of the ERK1/2 pathway, which targets 90-kDa ribosomal s6 kinase 1 (p90RSK) (Kir et al., 2011). This signaling peptide then interacts with glycogen synthase kinase (GSK) 3α and GSK3β. GSK3α and GSK3β are negative regulators of glycogen synthesis and suppress the action of glycogen synthase (GS). GS is inactive when phosphorylated and there is no synthesis of glycogen. Therefore, through phosphorylation of GSK3α and GSK3β, FGF19 prevents GS phosphorylation and maintains active glycogen synthesis. This function of FGF15/19 acts in parallel with the activity of insulin that is also capable of phosphorylating GSK3α and GSK3β at the same residues (Ser^{21} and Ser^{9}, respectively) (Sutherland, Leighton and Cohen, 1993). However, insulin acts on these proteins through the Akt pathway.

The aberrant production of glucose through gluconeogenesis is a hallmark characteristic of metabolic syndrome and diabetes (Hatting, Tavares, Sharabi et al., 2018). The ability of FGF15/19 to suppress gluconeogenesis is likely a key component to improve glucose control in mouse models of obesity. In mice, FGF15/19 suppresses the expression of key gluconeogenic genes including glucose-6-phophatase (*G6pase*) and phosphoenoylpyruvate kinase (*Pepck*) following 6 hr infusion of either peptide (Potthoff, Boney-Montoya, Choi et al., 2011). Based on promoter binding studies, direct gene regulation occurs through the ability of cAMP regulatory element-binding protein (CREB) being able to bind to the promoter of either gene. In addition, CREB also downregulates expression of a key transcription factor in metabolism, peroxisome proliferator-activated receptor gamma coactivator (PGC-1α), which also displays reduced binding to *G6pase* and *Pepck*. As of yet, the mechanism driving the dephosphorylation of CREB in this pathway is not fully known. Some research into CREB target gene silencing by FGF19 suggests that SHP binds to CREB, which can recruit histone methylase LSD1 causing epigenetic silencing of CREB target genes (Byun, Kim, Zhang et al., 2017). However, this mechanism does not entirely align with observed Co-IP of CREB and PGC-1α promoter binding data within *G6Pase* and *Pepck* (Potthoff et al., 2011). This suggests two separate mechanisms imparting repression of gluconeogenesis, but more research on these observations is needed.

Independent of the hepatic role of FGF19 on glucose homeostasis, FGF19 binding in the brain confers an additional level of control over serum glucose concentrations through pathways in both the forebrain and hindbrain. In rats with diet induced obesity, injection of FGF19 in the third cerebral ventricles lowers blood glucose without increasing release of insulin (Ryan, Kohli, Gutierrez-Aguilar et al., 2013). A similar glucose lowering effect occurred in *ob/ob* mice administered intracerebroventricular (ICV) FGF19 injection (Morton, Matsen, Bracy et al., 2013). Unlike mice given FGF19 i.v., ICV administered mice have reduced *G6Pase* mRNA, but no change to their *Pepck* mRNA levels and no increase in glycogen synthesis, providing insight into divergent mechanisms within the brain and liver over glucose regulatory control. Detailed examination of the neurons within the arcuate nucleus of the hypothalamus determined that the neuronal targets of FGF19 are not localized in the lateral melanocortin proopiomelanocortin (POMC) neuronal cells. Rather, FGF19 can activate ERK1/2 signaling in the dorsomedial hypothalamic nucleus to suppress agouti-related peptide (AgRP)/ neuropeptide Y (NPY) neuronal activity (Marcelin, Jo, Li et

al., 2014). The downstream activity of hypothalamic activation by FGF19 was mapped out in rats with streptozotocin induced type 1 diabetes (T1DM). ICV injection of FGF19 proved effective in decreasing serum glucose concentrations in an insulin-independent mechanism (Perry et al., 2015). The rats had markedly reduced adrenocorticotropic hormone (ACTH). The downstream reduction of circulating corticosterone and subsequent decreased lipolysis and acetyl CoA levels suppresses hepatic glucose production. Research that is more recent identified the dorsal motor nucleus of the vagus (DMV) as expressing both FGFR1 and KLB. Direct targeting of the DMV by 4th ventricle administration of FGF19 reduced serum glucose confirming a hindbrain pathway of FGF19 (Wean and Smith, 2021). It is plausible that FGF19 suppresses central vagal circuitry involved in vago-vagal reflexes, including glucose regulatory circuits within gut-brain-liver axis.

Diabetic mice (*db/db*) are unable to reduce serum glucose levels when administered FGF15, but effectively do so with FGF19 administration, which is due to FGF19's ability to bind to FGFR1c in peripheral tissues (Zhou et al., 2017). Adipocytes exclusively express FGFR1 among all FGFRs and express KLB. Administration of FGF19 to adipocytes increases phosphorylation of FRS2α and ERK1/2. Glucose uptake is elevated in adipocytes exposed to FGF19 and knockdown of *Klb* suppresses glucose uptake (Kurosu et al., 2007,Hansen, Vienberg, Lykkegaard et al., 2018). Further confirmation of FGF19-activiated glucose uptake in adipocytes was observed in DIO mice with adipocyte specific knockout of *Klb* (Lan et al., 2017). During a euglycemic-hyperinsulemic clamp, glucose infusion rate was significantly higher in wild-type mice after FGF19 infusion compared to $KLB^{-/-}$. Additionally, whole body glucose uptake increased during FGF19 infusion. However, some data conflicts with the ability of FGF19 to facilitate glucose uptake. A study by Anotonellis et al. did not see any increase in glucose uptake in DIO mice in white adipose tissue in either the absence or presence of insulin. There was a synergistic effect on glucose uptake in brown adipose tissue with FGF19 and insulin administration, however, FGF19 administered alone did not enhance glucose uptake in brown adipose tissue (Antonellis, Droz, Cosgrove et al., 2019). There is not any direct study of FGF19 increasing glucose transporters (GLUT) in adipocytes, but it is highly likely that, like FGF21 which shares the same FGF1c/KLB binding in adipocytes, FGF19 can increase GLUT1 in adipocytes (Ge, Chen, Hui et al., 2011). In pregnant mice, FGF19 can up regulate expression of the glucose transporter, GLUT4, and increase phosphorylation of the insulin signaling molecule, IRS1 and perhaps similar activation in adipocytes is present (Zhao, Wang, Li et al., 2021).

The action of FGF19 to reduce circulating glucose levels is through hepatic, central, and peripheral targeting but there are gaps in our understanding of glucose uptake from FGF19 signaling. Much of the peripheral impact of glucose uptake from FGF19 is focused on adipocytes. It is established that both the brain and muscle are targets of FGF19 and glucose-utilizing tissues. However, the exact contribution they impart on glucose uptake, mediated by FGF19, is unknown. Despite this gap, the ability of FGF19 to reduce serum glucose concentration does present exciting translational possibilities. In obese patients that receive roux-en-y gastric bypass surgery, rapid increases in bile acids and FGF19 are observed postoperatively (Sachdev, Wang, Billington et al., 2016,Gerhard, Styer, Wood et al., 2013,Jansen, van Werven, Aarts et al., 2011). There is some suggestion that this increase in FGF19 directly promotes resolution in type 2 diabetes suppressing gluconeogenesis

and improving peripheral glucose uptake (Gerhard et al., 2013,Bozadjieva, Heppner and Seeley, 2018,Pournaras, Glicksman, Vincent et al., 2012). Yet, this finding is not supported in all human studies and is still a topic of debate (Harris, Smith, Mittendorfer et al., 2017,Jorgensen, Dirksen, Bojsen-Moller et al., 2015). However, this presents a unique potential opportunity for research into FGF19 and what role direct administration of the hormone may have in improving glucose control in patients with type 2 diabetes.

6.2.2 Lipid Metabolism—White and brown adipose tissue express FGFR1c and KLB and are therefore potential targets for FGF19 activity (Fon Tacer et al., 2010). FGF19 regulation of adiposity was first observed in the development of the transgenic mice overexpressing the gene. These mice had lower body weight and higher lean mass relative to normal mice (Tomlinson et al., 2002). In various models of obesity in mice, FGF19 also promotes reduced adiposity. In DIO mice fed a diet of high fat, high fructose, and high cholesterol AAV overexpression of reduced accumulation of hepatic lipids and expression of lipogenic enzymes (Zhou, Learned, Rossi et al., 2017). In addition, there were increased un-oxidized cardiolipins in the inner mitochondrial membrane. These cardiolipins are essential for mitochondrial function and efficient energy conversion, therefore providing an additional mechanism to facilitate lipid clearance in these mice (Dudek, 2017). In leptin deficient *ob/ob* mice fed a high fat diet, transgenic overexpression of FGF19 can reduce body weight and fat pad mass (Fu et al., 2004). However, in *ob/ob* leptin deficient mice fed standard chow, there were no changes in body weight with exposure to FGF19 (Fu et al., 2004,Wu et al., 2013). Interestingly, despite the chow fed *ob/ob* mice not losing any weight, they did have increased serum concentrations of triglyceride and cholesterol (Wu et al., 2013). Whereas initially this would appear paradoxical to have a phenotype that can drive a reduction in fat mass, but also cause elevations in serum lipids, it is suggested this is through the dual functions of FGF19. The hepatic role of FGF19 in suppressing bile acid metabolism leads to increased cholesterol and triglycerides, while the metabolic effects on adiposity target utilization of deposited lipid in peripheral tissue. In support of this hypothesis, generation of a C-terminal domain modified FGF19, which leads to loss of FGF1c binding, still increases cholesterol and triglyceride concentration in *ob/ob* mice, suggesting it is a FGFR4-dependent effect. In humans, it is not clear if the same response will be present. In clinical trials, the use of the FGF19 analog NGM282 reduced triglycerides by up to 47.3 mg/dl compared to baseline, but did see an increase in cholesterol levels. (Harrison, Rinella, Abdelmalek et al., 2018,Rinella, Trotter, Abdelmalek et al., 2019). Also in humans, short term treatment with bile acid sequestrant, cholestyramine, decreased FGF19 and caused a transient increase in triglycerides. However, treatment in subjects for up to one month still observed an increase in FGF19 concentrations, but triglycerides were unchanged (Sjoberg, Straniero, Angelin et al., 2017).

Despite the clear effect that overexpression of FGF19 has on the reduction of hepatic lipids, there is conflicting data on hepatic lipid accumulation from deletion of FGF15. *Fgf15*$^{-/-}$ mice fed a high fat diet for six months did not differ in the degree of hepatic steatosis or inflammation in the liver. Interestingly, they had a reduction in fibrosis compared to HFD fed controls. The KO mice did have elevated serum triglycerides, alterations in lipogenic gene expression, and altered bile acid homeostasis (Schumacher, Kong, Pan et al., 2017).

However, a similarly designed study found slightly different results with *Fgf15*$^{-/-}$ mice fed high fat diets developing elevated hepatic triglycerides and increased palmitic acid-derived ER stress (Alvarez-Sola, Uriarte, Latasa et al., 2017). Mice that lack the KLB receptor are resistant to diet induced obesity due to an increase in their energy expenditure. They do display altered bile acid composition, suggesting that there are direct changes to FGF19 signaling (Somm, Henry, Bruce et al., 2017). However, there is weak binding that can occur with FGFR4 alone that may contribute to partial signaling of FGF15 (Yang et al., 2012). Though in a similar result, FGFR4 KO mice fed a high fat diet do have lower weight gain than controls and have similar liver triglyceride concentrations. They do, like KLB KO mice, have a higher bile acid pool and larger fecal bile acid output.

The mechanism of how FGF15/19 causes a decrease in lipogenic genes in the liver has only recently started to become clear (Figure 4). Early studies show that peroxisome proliferated associated receptor gamma-2 (PPARγ-2) a key transcriptional regulator of lipogenic genes is suppressed by FGF19 (Alvarez-Sola et al., 2017), along with other associated genes such as fatty acid synthase, sterol regulatory binding protein 1, acyl coA carboxylase and others. A study by Kim et al. recently found that SHP binding regions overlap CpG islands of lipogenic genes (Kim, Seok, Zhang et al., 2020). FGF19 phosphorylation of SHP at these sites allow SHP to recruit dna methyl transferase 3A (DMNT3A) to these regions. DMNT3A increased methylation at the CpG sites represses the expression of the lipogenic genes.

Our current understanding of how adiposity is regulated by FGF19 in the liver is better developed than our current understanding in peripheral tissues. Whereas there is considerable information on the role FGF19 exerts in reduction of adiposity from changes in energy metabolism, which will be discussed in detail in the section below, there is limited data on gene expression and regulation of lipogenic activity of FGF19 in adipocytes. Specifically, research into white adipose tissue, which expresses both FGFR1/KLB, is needed for a better understanding of applicability to human obesity.

6.2.3 Energy Metabolism—Like glucose metabolism, energy metabolism is a general term for multiple pathways that balance energy expenditure through changes in activity and metabolic rate, and energy accretion through food intake and macronutrient preference. In humans, obesity can cause a decrease in circulating FGF19 levels (Gallego-Escuredo, Gomez-Ambrosi, Catalan et al., 2015). Whether the decrease in FGF19 is a cause of obesity, or an effect of metabolic changes and elevated inflammation is not entirely clear. However, the animal data strongly supports a direct role of FGF19 in preventing obesity and controlling whole body metabolism. FGF19 overexpression in normal, healthy mice decreases body weight through increased oxygen consumption (VO_2), a marker of activity, but does not change respiratory quotient (RQ), an indicator of macronutrient utilization (Tomlinson et al., 2002). These mice are more active, but do not show an altered preference for either fat or carbohydrate intake. They do however increase total food intake, likely as a result of overall increased activity-mediated energy expenditure. In most mouse models of obesity, FGF19 leads to a similar positive effect on body weight. DIO mice administered either AAV-FGF19 or daily iv FGF19 injection lose weight and increase their VO_2 uptake, accompanied by higher energy expenditure (Lan et al., 2017,Zhou et al., 2017,Fu et al.,

2004). Both transgenic overexpression of FGF19 or daily administration is effective in reducing body weight of *ob/ob* leptin deficient mice (Fu et al., 2004). Though RQ was not examined in all studies, mice that consumed a high fat diet had a lower RQ after FGF19 administration, suggesting that FGF19 causes a shift to greater fat utilization (Fu et al., 2004). Not all mouse models of obesity respond to FGF19 treatment. In *db/db* diabetic mice, glucose concentrations were markedly reduced, but there was no change in body weight after 25 weeks for FGF19 treatment (Zhou et al., 2017).

Investigations into the FGF19-mediated decrease in body weight has focused mostly on the role of elevated metabolic rate and activity, based on the findings of initial mouse studies showing high VO_2 and energy expenditure. In adipose tissue, energy expenditure can be elevated through an increase in thermogenesis. Brown adipose tissue has high thermogenic potential and in both mice and humans increases energy expenditure and acts as a protective mechanism against cold stress (van der Lans, Hoeks, Brans et al., 2013,van Marken Lichtenbelt, Vanhommerig, Smulders et al., 2009,Cannon and Nedergaard, 2004). Exposure of mice to cold leads to adipose remodeling with white adipose tissue browning as a protective mechanism. A recent study found that AAV-FGF19 administration to mice increased subcutaneous white adipose tissue browning and increased brown adipose tissue thermogenic genes uncoupling protein 1 (*Ucp1*), iodothyronine deiodinase 2 (*Dio2*), and *Ppargc1a (*Moron-Ros, Uriarte, Berasain et al., 2021). Additionally, $Fgf15^{-/-}$ mice were unable to transition white adipose tissue to brown adipose tissue. Interestingly, FGF15/19 have no effect on adipose tissue that is already brown. This result suggests that FGF15/19 are necessary to drive adipocyte remodeling to brown adipose tissue, but do not have an active effect in driving thermogenesis. This result contrasts with other reports on the function of FGF19 in adipocytes. A study be Antonellis et al found there is an increase in uncoupling protein 1 (UCP1) in brown adipose tissue of mice following iv administration of FG19, which increases thermogenesis and weight loss (Antonellis et al., 2019). However, $Ucp1^{-/-}$ mice still lose weight following FGF19 administration. Possibly, following FGF19 administration, weight loss comes from impaired fat absorption due to a decrease in CYP7A1 generated luminal bile acids.

An alternative mechanism that likely plays a much larger role in reducing body weight following FGF19 administration is from central nervous system reduction of metabolism in the hypothalamus. ICV FGF19 injection in mice causes an increase in VO2 consumption (Fu et al., 2004). In both rats and mice on high fat diets, FGF19 ICV administration causes a reduction in food intake and body weight (Ryan et al., 2013,Marcelin et al., 2014). Though these studies give a good indication for the action of FGF19 in the brain, they still do not clarify if there is a strictly tissue-dependent role of FGF19 on weight reduction. The best indication thus far on the tissue specificity for FGF19-meditated weight regulation is from research conducted by Lan et al. using tissue specific knockout of *Klb (Lan et al., 2017)*. Using mice with $Klb^{-/-}$ in the liver, adipose, and brain, the researchers were able to isolate various metabolic roles of FGF19 to each tissue. They observed that $Klb^{-/-}$ liver or adipose mice with diet induced obesity still lost weight following FGF19 administration. Only mice with $Klb^{-/-}$ in the brain failed to lose weight following FGF19 administration. The activation of FGFR1c/KLB in the brain did however increase sympathetic outflow to

brown adipose tissue, so at least a partial mechanism of brain-mediated regulation on weight loss by FGF19 takes place in brown adipose.

Given the conflicting data in mouse models, it is difficult to draw conclusions over the mechanism through which FGF19 increases energy expenditure and facilitates weight loss. Though studies that show a UCP1-independent effect combined with research showing the weight loss in intestinal $Klb^{-/-}$ mice, give the best indication that much of the FGF19 weight loss effect is not centralized in the adipocyte in mice. However, the clinical impact of FGF19 on energy expenditure is still unknown. There are no studies that have appropriately looked at changes in VO_2 consumption and energy expenditure in humans following FGF19 administration.

6.3 Growth Factor: Protein Synthesis and Tumorigenesis

The primary function of most paracrine FGFs is to facilitate growth and development from the embryonic stage to adulthood. FGF15/19 shares this feature with the rest of the superfamily and can function as a growth factor in both normal cellular responses to nutrient signaling and cellular repair, but also can have aberrant activity leading to the development of neoplasia. In the normal fed state, FGF19 promotes protein synthesis through insulin-independent mechanisms (Figure 5). Mice administered FGF19 i.p. have increased hepatic global protein synthesis rates, increased albumin, and increased liver weight (Kir et al., 2011). The primary pathway for this process starts with FGF15/19 binding to FGFR4/KLB and activating ERK1/2 and then phosphorylation of MAPK interacting protein kinases 1 (Mnk1) at Thr^{197} and Thr^{202}. Downstream of Mnk1 is phosphorylation of eukaryotic initiation factor 4e (eIF4E) at Ser^{209}. eIF4e is the cap-binding protein that is part of the recruitment complex for ribosomes for the translation of mRNA. Phosphorylation of eIF4E activates it, to enhance protein translation. Parallel to activation of eIF4E, ERK1/2 activation also enhances phosphorylation of residues Ser^{235} and Ser^{236} of ribosomal protein S6 (rpS6). Phosphorylation of rpS6 improves global protein synthesis by activating cap-dependent translation (Meyuhas, 2015). The direct upstream mediator of rpS6 is p90RSK, which is the target of ERK1/2 signaling from FGF19. Importantly, this pathway is distinct from insulin, which can also activate rpS6, but signals through p70S6K, rather than p90RSK. Thus, this pathway enhances protein synthesis signaling, but independently of mTOR. More recently, it was suggested that FGF19 can activate S6 through a second independent pathway to create a two-pronged activation of S6 (Wan et al., 2016). Activation occurs through the Ral complex activating mammalian target of rapamycin complex (mTORC)-1 and p70S6K. This finding does somewhat contrast the initial research identifying p90RSK as the main target of FGF19. In the earlier study, treatment of HepG2 liver cells with rapamycin did not prevent FGF19-mediated phosphorylation of rpS6 (Kir et al., 2011). This suggested that the mechanism is entirely mTOR independent. Likely there will need to be more studies to clearly define whether FGF19 activates rpS6 through two redundant pathways, or has a single unique target pathway.

FGF19 stimulates protein synthesis in other tissues besides the liver, where in skeletal muscle, FGF19 has anabolic effects. FGF19 can increase muscle fiber size and prevent against skeletal muscle atrophy (Benoit et al., 2017). Both *in vivo* and *in vitro*, FGF19-

mediated protein synthesis signals through activation of the mTOR – S6K1 pathway. Recent research has also shown that obesity induced muscle atrophy can be reduced with FGF19 administration via activation of the AMPK/SIRT-1/PGC-alpha pathway (Guo, Li, Tian et al., 2021).

In addition to skeletal muscle and hepatic protein synthesis, FGF15/19 is important in liver growth and regeneration. *Fgf15*$^{-/-}$ or *Fgfr4*$^{-/-}$ in mice impairs their capacity to regenerate liver following partial hepatectomy (Kong, Huang, Zhu et al., 2014,Uriarte, Fernandez-Barrena, Monte et al., 2013,Padrissa-Altes, Bachofner, Bogorad et al., 2015). In *Fgf15*$^{-/-}$ mice, there is a reduction in ERK signaling and an impairment to induce the key regulators of cytokine transcription signal transducer and activator of transcription 3 (STAT3) and nuclear-localized nuclear factor kappa B (NF-κB) (Kong et al., 2014). Cytokine response is important for priming the liver to activate regeneration and the loss of this feature by FGF15 may impair the early signaling necessary for priming liver regeneration. In a recent human clinical study examining the role of FGF19 during early phase liver regeneration, there was no change in FGF19 expression post-hepatectomy, but there was a large increase in bile acid production, suggesting low FGF19 activity (Koelfat, van Mierlo, Lodewick et al., 2021). The authors concluded that FGF19 might only play a minor role in human liver regeneration and that bile acids may be the more relevant molecules regulating early phase events. Thus, more detailed molecular analysis of FGF19 during liver regeneration would be needed to for definitive conclusions.

Even if not specific to a function in liver regeneration, it is clear FGF19 does play an important role in hepatic growth. Ectopic overexpression of FGF19 in skeletal muscle of mice causes hepatic tumor growth (Nicholes et al., 2002). Hepatic tumorigenesis also occurs in mice administered an AAV-FGF19 vector (Zhou et al., 2017); however, in the same study mice administered AAV-FGF15 did not develop tumors. Thus, identifying FGF19 tumorigenic effect as orthologue-specific. The tumorigenic effect is not isolated to FGF19 treatment in mice, as FGF19 expression in patients correlates with tumor progression and incidence of hepatocellular carcinoma (Miura, Mitsuhashi, Shimizu et al., 2012). FGF19-mediated tumorigenesis can be blocked as both *FGFR4*$^{-/-}$ mice and mice treated with an antibody targeting FGFR4, do not develop hepatic tumors when FGF19 is overexpressed (French, Lin, Wang et al., 2012). This result is particularly interesting as it suggests that FGF15 and FGF19 binding to FGFR4 differs enough to alter the magnitude of downstream signaling cascades and result in divergent biological effects.

FGF19 functions in an autocrine feed forward loop in hepatocellular carcinoma (HCC). FGF19 activates signaling pathways that lead to the progression of HCC and then tumor cells upregulate expression of FGF19 to facilitate continued growth (Kang, Haq, Sung et al., 2019,Sawey, Chanrion, Cai et al., 2011,Latasa, Salis, Urtasun et al., 2012,Ahn, Jang, Shim et al., 2014). The same autocrine feed forward function is also active in gall bladder cancer, another site of both FGF19 expression and FGFR4 receptors (Chen, Liu, Liu et al., 2021). FGF19 and FGFR4 target extra hepatic cancers as well including colon cancer (Pai, Dunlap, Qing et al., 2008,Heinzle, Gsur, Hunjadi et al., 2012), lung cancer (Li, Li, Han et al., 2020), head and neck squamous cell carcinoma (Gao, Lang, Zhao et al., 2019) and potentially breast (Tiong, Tan, Choo et al., 2016), and ovarian cancers (Zaid, Yeung, Thompson et al.,

2013). It is out of the scope of this review to cover all the pathways and mechanisms FGF19 activates to promote all the types of associated cancer. FGF19/FGFR4 activity in HCC functions through multiple pathways to enhance tumorigenesis and metastasis (Goetz and Mohammadi, 2013). Activation of the Raf-Ras-MAPK pathway generates a mitogenic cell response. Cell motility is enhanced through phospholipase Cγ activation of protein kinase C. Suppression of apoptosis occurs through PI3K-AKT pathways. FGF19 can also enhance the metastatic potential for HCC through induction of epithelial–mesenchymal transition (EMT) via activation of the GSK3-cantenin pathway (Zhao, Lv, Liang et al., 2016). Additionally by activation of the STAT3 pathway through JAK-STAT signaling, FGF19 can enhance tumor growth (Zhou, Wang, Phung et al., 2014).

7. Therapeutics

With a functional understanding of the biological pathways FGF19 targets and the structure/function relationship of FGF19, there is great interest in use of the FGF19 pathway to treat diseases associated with bile acid homeostasis, metabolism and cancers. The two predominant approaches to pharmaceutically increase circulating FGF19 is either directly by hormone administration or indirectly through activation of the FXR pathway. There are several drug compounds that function as FXR agonists to activate the FGF19 pathway through FXR and are either FDA approved (e.g. Obeticholic acid) or in clinical trials (e.g. Tropifexor). However, given that these drugs have a greater array of biological effects through FXR than to just increase FGF19, they are outside the scope of this review.

Native human FGF19 is not an ideal candidate for activation and treatment of diseases related to cholestasis and metabolism given its mitogenic properties. Various analogues are in development to mimic the effects of FGF19 on bile suppression and glucose/lipid metabolism that lack the mitogenic effect. One such peptide is NGM282 (Aldafermin), which has three amino acid substitutions (A30S, G31S, and H33L) and five-amino acid deletions in the N-terminal region of FGF19 (Zhou et al., 2014,Luo, Ko, Elliott et al., 2014). Early mouse studies showed that NGM282 could suppress bile acid synthesis and reduce hepatic lipotoxicity associated with obesity in mice (Zhou et al., 2017,Zhou, Learned, Rossi et al., 2016). Currently in human trials, NGM282 can reduce bile acid synthesis is patients with primary sclerosing cholangitis and reduce markers of fibrosis, but does not reduce serum markers of liver injury, such as alkaline phosphatase (Hirschfield, Chazouilleres, Drenth et al., 2019,Sanyal, Ling, Beuers et al., 2021). In clinical trials for obesity-associated non-alcoholic steatohepatitis, NGM282 treatment can reduce hepatic lipid content and improve markers of fibrosis, without any indication of tumorigenesis (Harrison et al., 2018,Rinella et al., 2019,Sanyal et al., 2021,Harrison, Neff, Guy et al., 2021). Other than NGM282, there are additional variants that have modified single point mutations in FGF19 binding domains to FGFR4 (Y115A), HS (K149A), and KLB (D198A) display decreasing mitogenic signaling, respectively, while still reducing bile acids synthesis (Niu et al., 2020). Interestingly, these single point mutations are enough to impair formation of a quaternary structure of two FGFR4/KLB dimers, limiting the signaling potential of FGF19.

8. Conclusions

The field of FGF19 research is still rapidly expanding. Our understanding of the signaling events that mediate FGF19 action and the various target tissues and signaling pathways of FGF19 are still being delineated. There is still a limited literature defining the physiological and metabolic function of FGF19 during early development after birth or at later stages in life, such as aging. There are still gaps in our knowledge of signaling pathways and the exact role of the brain, adipose, and liver for regulation of whole body metabolism and glucose regulation. One issue of particular concern is how well studies in mice administered FGF19 translate to the human response of FGF19 given the species difference in receptor expression of FGFR1c-FGFR3c. This limitation can be overcome with use of more translational preclinical models, like the pig, that naturally express FGF19 and have receptors that more closely match human FGFRs and KLB.

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Abbreviations:

FGF	fibroblast growth factor
HS	heparin sulfate
FGFR	fibroblast growth factor receptor
KLB	β-Klotho
Ig	immunoglobulin
KLA	α-Klotho
FXR	farnesoid x receptor
CDCA	chenodeoxycholic acid
FXRE	FXR-responsive binding elements
PXR	pregnane x receptor
LCA	lithocholic acid
ATF4	activating transcription factor 4
AARE	amino acid response element
SREBP2	sterol regulatory element-binding protein 2
Klf15	Kruppel-like factor 15
PI3K	phosphoinositide 3-kinase

Akt	protein kinase B
GATA4	GATA binding protein 4
GR	glucocorticoid receptor
CA	cholic acid
CYP7A1	cytochrome P450 7A1
α-MCA	α-muricholic acid
HCA	hyocholic acid
BSEP	bile salt efflux pump
DCA	deoxycholic acid
SHP	small heterodimeric partner
LRH-1, Nr5a2	liver receptor homolog 1
HNF4	hepatocyte nuclear factor 4 alpha
FRS2α	FGFR substrate 2 alpha
OSTα/β	solute transporter alpha/beta
MRP2	multidrug resistance protein 2
MAPK/ERK1/2	mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2
TFEB	transcription factor EB
mTOR	mammalian target of rapamycin
PBC	primary biliary cirrhosis
TGR5	G-protein-coupled bile acid receptor
S1PR2	sphingosine 1 phosphate receptor 2
AAV	adeno-associated virus
p90RSK	90-kDa ribosomal s6 kinase 1
S6K1	ribosomal protein S6 kinase beta-1
GSK	glycogen synthase kinase
G6pase	glucose-6-phophatase
Pepck	phosphoenoylpyruvate kinase
CREB	cAMP regulatory element-binding protein

PGC-1α	peroxisome proliferator-activated receptor gamma coactivator
ICV	intracerebroventricular
POMC	proopiomelanocortin
AgRP	agouti-related peptide
NPY	neuropeptide Y
T1DM	type 1 diabetes
ACTH	adrenocorticotropic hormone
DMV	dorsal motor nucleus of the vagus
DIO	diet induced obesity
PPARγ-2	peroxisome proliferated associated receptor gamma-2
DMNT3A	dna methyl transferase 3A
RQ	respiratory quotient
UCP1	uncoupling protein 1
Mnk1	MAPK interacting protein kinases 1
eIF4E	eukaryotic initiation factor 4e
rpS6	ribosomal protein S6
mTORC	mammalian target of rapamycin complex
STAT3	signal transducer and activator of transcription 3
NF-κB	nuclear factor kappa B
HCC	hepatocellular carcinoma

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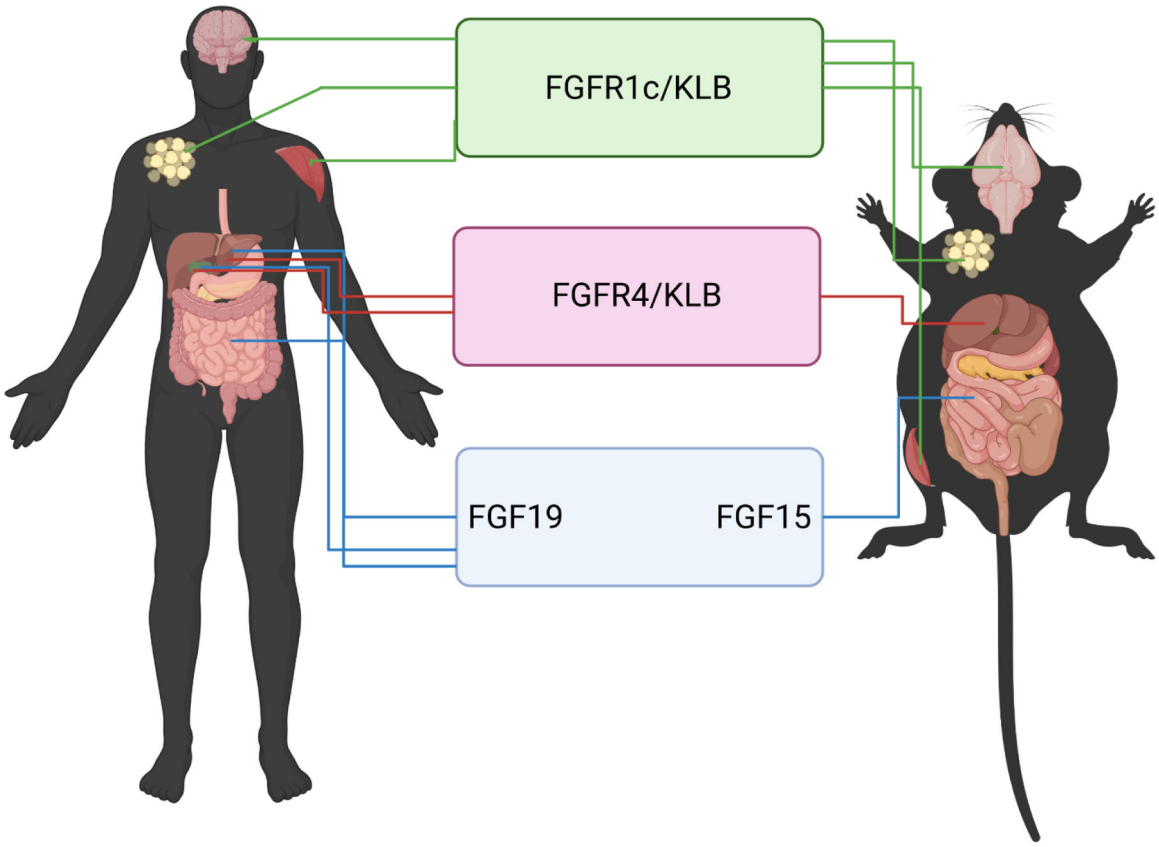

Figure 1.
Expression pattern of FGF15/19, FGFR4, FGF1c, and KLB in human and mouse. Fibroblast growth factor (FGF), fibroblast growth factor receptor (FGFR), β-Klotho (KLB)

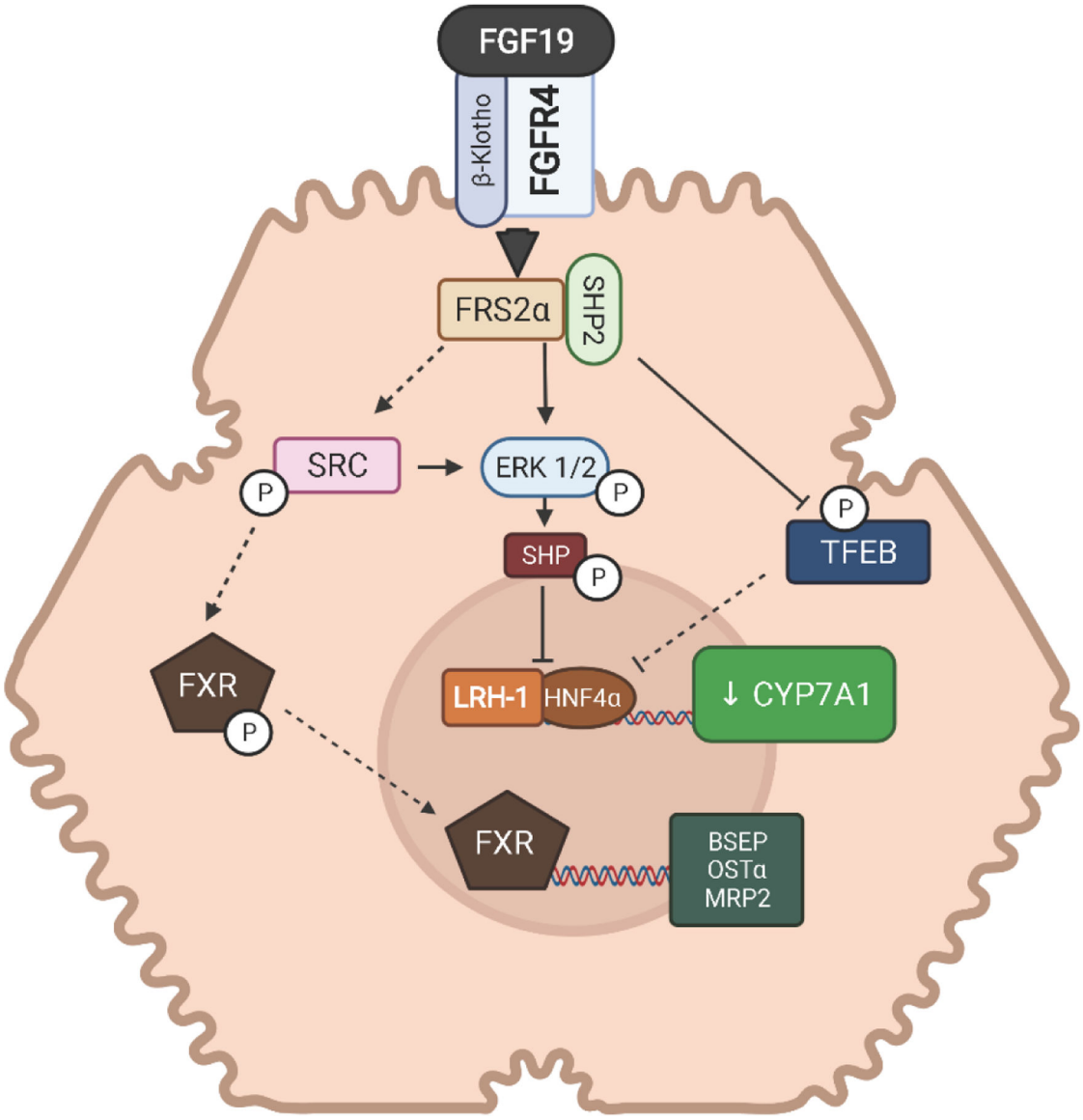

Figure 2.

Bile acid signaling of FGF19-FGFR4 in the liver. fibroblast growth factor (FGF), fibroblast growth factor receptor (FGFR), β-Klotho (KLB), farnesoid x receptor (FXR), cytochrome P450 7A1 (CYP7A1), bile salt efflux pump (BSEP), small heterodimeric partner (SHP), liver receptor homolog 1 (LRH-1), hepatocyte nuclear factor 4 alpha (HNF4), FGFR substrate 2 alpha (FRS2α), solute transporter alpha/beta (OSTα/β), multidrug resistance protein 2 (MRP2), extracellular signal-regulated kinase 1/2 (ERK1/2), transcription factor EB (TFEB). Dashed lines represent potential pathways not fully confirmed experimentally.

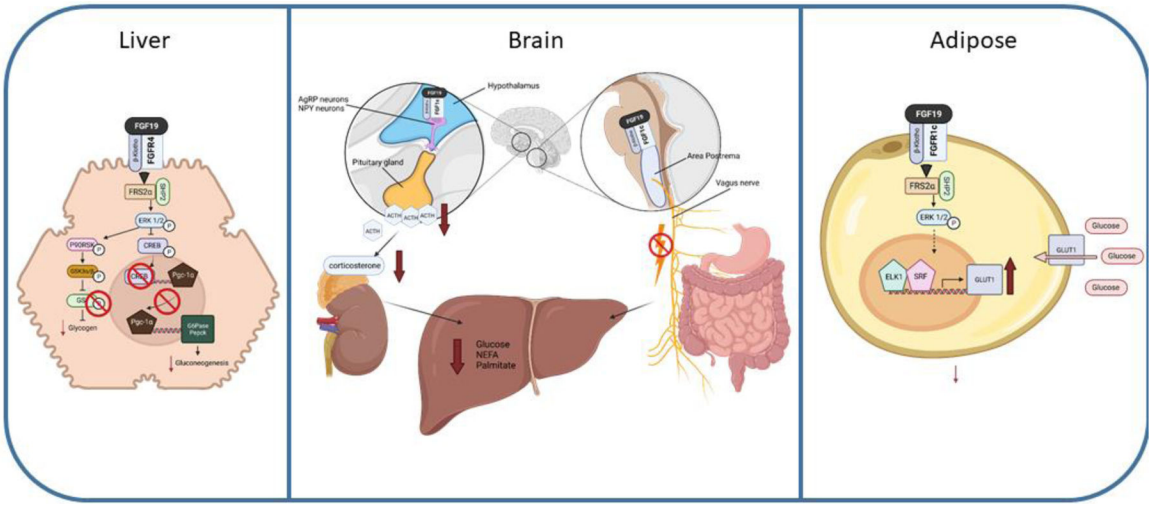

Figure 3.

FGF19 regulation of glucose homeostasis in the liver, brain, and adipose tissue. fibroblast growth factor (FGF), fibroblast growth factor receptor (FGFR), β-Klotho (KLB), FGFR substrate 2 alpha (FRS2α), extracellular signal-regulated kinase 1/2 (ERK1/2), 90-kDa ribosomal s6 kinase 1 (p90RSK), glycogen synthase kinase (GSK), glucose-6-phophatase (G6pase), phosphoenoylpyruvate kinase (Pepck), cAMP regulatory element-binding protein (CREB), peroxisome proliferator-activated receptor gamma coactivator (PGC-1α), agouti-related peptide (AgRP), neuropeptide Y (NPY), adrenocorticotropic hormone (ACTH), erythroblast transformation specific transcription factor (ELK1), serum response factor (SRF), glucose transporter (GLUT), non-esterified fatty acid (NEFA). Dashed lines represent potential pathways not fully confirmed experimentally.

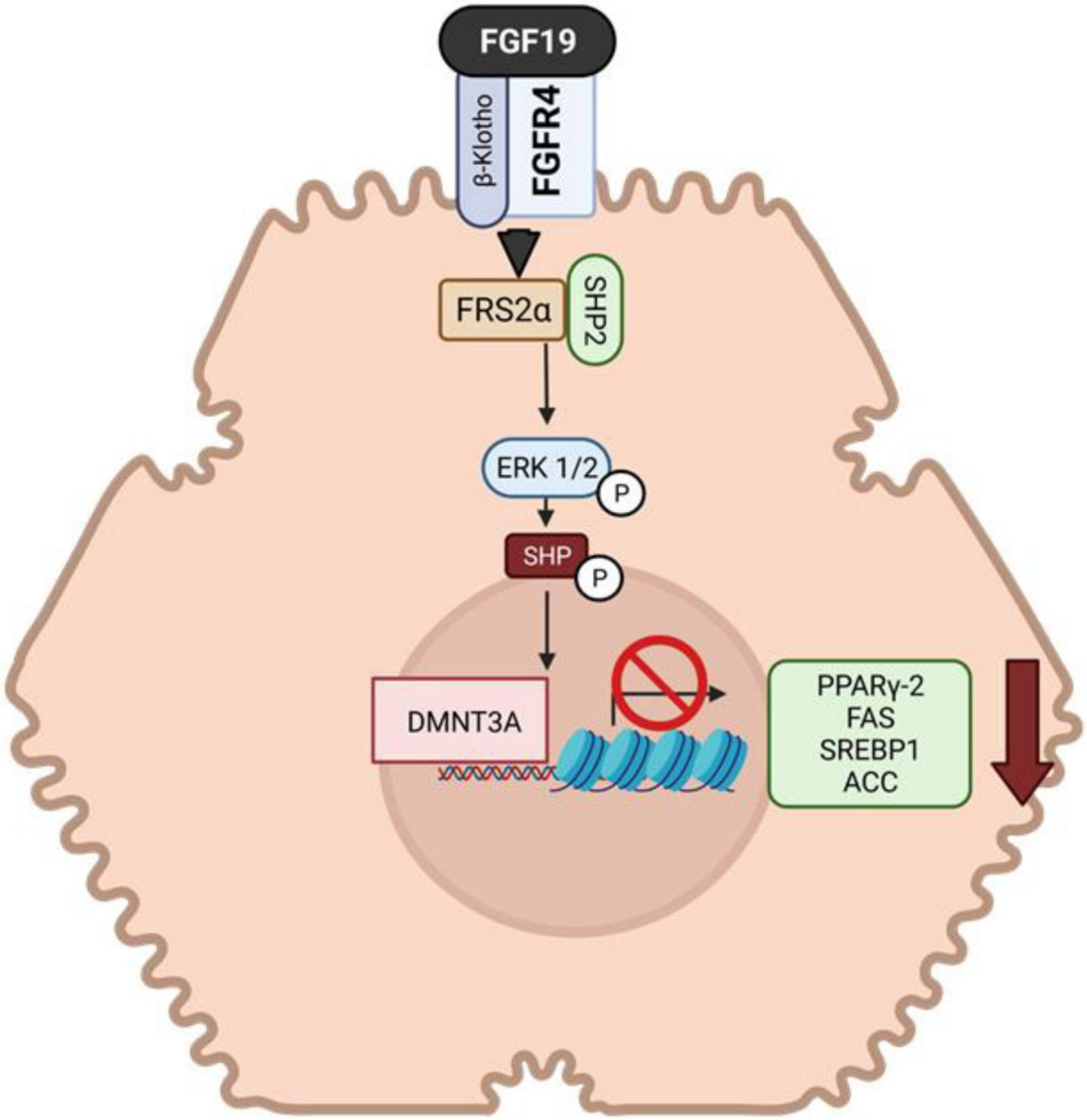

Figure 4.

FGF19 regulation of lipid homeostasis in the liver. fibroblast growth factor (FGF), fibroblast growth factor receptor (FGFR), β-Klotho (KLB), small heterodimeric partner (SHP), FGFR substrate 2 alpha (FRS2α), extracellular signal-regulated kinase 1/2 (ERK1/2), peroxisome proliferated associated receptor gamma-2 (PPARγ-2), dna methyl transferase 3A (DMNT3A), sterol regulatory element binding protein 1 (SREBP1), fatty acid synthase (FAS), acyl-coA carboxylase (ACC).

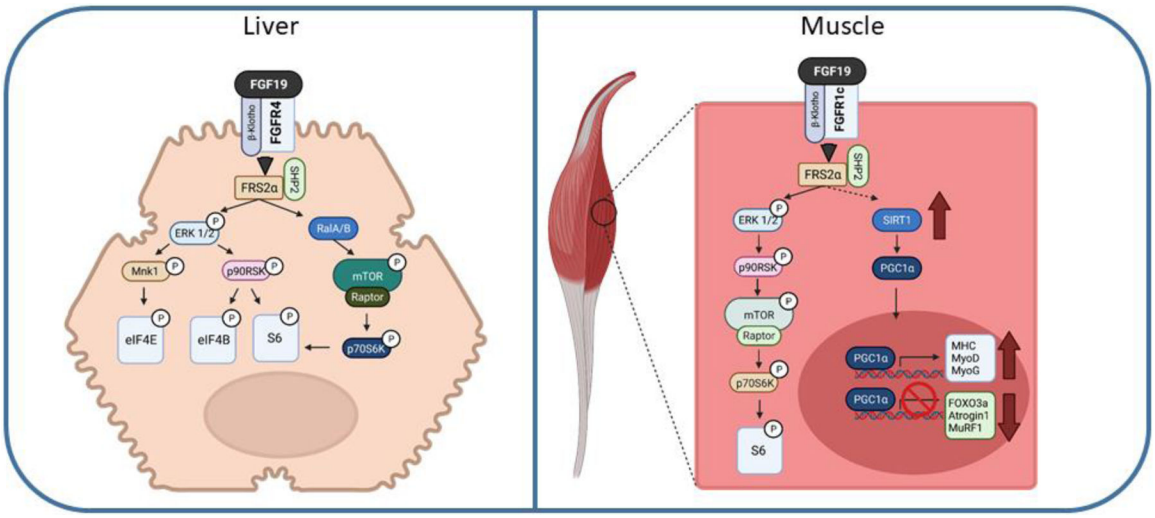

Figure 5.

FGF19 signaling in protein synthesis in the liver and skeletal muscle. fibroblast growth factor (FGF), fibroblast growth factor receptor (FGFR), β-Klotho (KLB), FGFR substrate 2 alpha (FRS2α), extracellular signal-regulated kinase 1/2 (ERK1/2), mammalian target of rapamycin (mTOR), regulatory-associated protein of mTOR (Raptor), 90-kDa ribosomal s6 kinase 1 (p90RSK), ribosomal protein S6 kinase beta-1 (p70S6K1), glperoxisome proliferator-activated receptor gamma coactivator (PGC-1α), MAPK interacting protein kinases 1 (Mnk1), eukaryotic initiation factor (eIF), ribosomal protein S6 (S6), sirtuin (SIRT), major histocompatibility complex (MHC), myoblast determination (MyoD), myogenin (MyoG), forkhead/winged helix box gene, group (FOXO), E3 ubiquitin-protein ligase (MuRF). Dashed lines represent potential pathways not fully confirmed experimentally.