

Review



Role of Fibroblast Growth Factor 19 in Maintaining Nutrient Homeostasis and Disease*

ZHANG Jing^{1,2}, LI Hua Ting¹, FANG Qi Chen^{1,#}, and JIA Wei Ping¹

Fibroblast growth factor 19 (FGF19) is a kind of gut-derived postprandial hormone. As an atypical member of the FGF family, FGF19 functions as an endocrine hormone except regulating cell growth and differentiation. FGF19 plays a key role in coordination of liver bile acid biosynthesis and gallbladder motility, and acts as a regulator of metabolic homeostasis, including strengthening insulin sensitivity, decreasing triglyceride concentration and reducing body weight. FGF19 is related with coronary artery disease and renal function. The multiple beneficial effects make FGF19 an attractive drug candidate for regulating bile acid homeostasis and treating metabolic disease. However, an important caveat is that FGF19 could stimulate proliferation which may be associated with cancer. Pharmacological study should focus on developing novel FGF19 analogues with potent metabolic effects but no proliferative effects of FGF19. This paper summarizes the recent advances in studies on FGF19.

Fibroblast growth factors (FGFs) are a group of proteins involved in various biological processes, such as development, repair, and metabolism^[1]. Currently, the human FGF family consists of 22 members which can be divided into 7 subfamilies according to their gene locus and action modes^[2], including the intracellular FGF11/12/13/14 subfamily, hormone-like (endocrine) FGF19/21/23 subfamily^[3], and canonical FGF subfamily containing FGF1/2/5, FGF3/4/6, FGF7/10/22, FGF8/17/18, and FGF9/16/20^[4-5]. Most FGFs play an important role in regulating cell growth and differentiation, while FGF19 together with FGF21 and FGF23 has no or mild mitogenic effects. However, it functions via systemic, hormone-like effects. FGF19 (the human ortholog of murine FGF15)^[6-7] is primarily secreted in the small intestine but regulates bile acid synthesis in the liver both in

rodents^[8] and in humans^[9], and regulates glucose, lipid and energy homeostasis.

DISCOVERY AND RECEPTORS

The human FGF19 was originally identified in the fetal brain^[6]. FGF19 shares 50% amino acid identity with its rodent ortholog, FGF15^[7], and they elicit similar effects on metabolic parameters in mice^[8,10]. FGF19 is mainly expressed in brain, skin, retina, gallbladder, small intestine, kidney, and umbilical cord^[6,11]. Typically, FGF binds to its receptors (FGFRs 1-4). This binding interaction needs the heparan sulfate glycosaminoglycan (HSGAG) cofactors which effectively activate the FGFR signaling^[12-14]. Its interaction with HSGAG can limit the FGF to the site of release^[13-14]. The affinity of FGF19 is weaker to heparan sulfate of the pericellular space than that of typical FGF and can thus serve as an endocrine hormone^[14-15]. The single-transmembrane containing protein β -Klotho from the Klotho family can interact with FGFRs 1-4 and stabilize the FGF-FGFR interaction^[16-19]. FGFRs are expressed extensively whereas β -Klotho is expressed in adipose, liver and pancreas, thus limiting the potential target tissues to the sites where both β -Klotho and appropriate FGFRs are expressed^[14-15,19]. FGF19 signaling through FGFR1c, FGFR2c and FGFR3c is dependent on the presence of β -Klotho. However, FGF19 can interact directly with FGFR4 without β -Klotho in a heparin-dependent manner. In a word, FGF19 activates FGFR4 signaling in the presence or absence of β -Klotho^[20].

MECHANISMS OF FUNCTIONS

Bile Acid Homeostasis

FGF19 is a negative feedback regulator of bile

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1. Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai 200233, China; 2. Department of Medicine, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

acid metabolism. Synthesized in the liver, bile acids are stored in the gallbladder and released into the small intestine where they play an essential role in dissolving dietary lipids, cholesterol, and fat-soluble vitamins^[21]. Endogenous bile acid ligands can activate the Farnesoid X receptor (FXR), a nuclear receptor acting as a regulator of bile acid biosynthesis and circulation^[22]. In response to the absorption of bile acids, the intestine produces FGF19 that acts to inhibit cholesterol 7 α -hydroxylase (CYP7A1), the first and rate-limiting enzyme in the bile acid biosynthetic pathway, which can be regulated by the FXR through small heterodimer partner (SHP) in the liver^[23-27] (Figure 1). It has been shown that FXR agonists can induce FGF19 in cultured human hepatocytes^[28]. FGF19 represses CYP7A1 in the liver by binding to the FGFR4/ β -Klotho receptor complex. The CYP7A1 expression and bile acid synthesis levels are higher in FGFR4-KO and β -Klotho-KO mice^[29-31]. FGF19 can regulate gallbladder filling besides bile acid synthesis. Normally in response to fasting, bile acids are stored in the gallbladder until they are needed for digestion, which cannot be observed in FGF15-KO mice with a virtually empty gallbladder^[32]. The gallbladder volume was greater than 10-fold increase in FGF15 knockout mice and 2-fold increase in wild-type mice after administration of recombinant FGF15 or FGF19^[32] (Figure 2), demonstrating that FGF19 plays an overarching role in the post-prandial refilling of gallbladder^[30,33] (Figure 1).

Glucose Metabolism

In addition to controlling the biosynthesis of bile acids, FGF19 regulates systemic glucose metabolism. An interesting function for FGF19 in regulating energy homeostasis is identified in FGF19 transgenic mice^[34]. The serum glucose and insulin levels are lower while the glucose tolerance and insulin sensitivity are higher in FGF19 transgenic mice than in wild-type littermates^[34] (Figure 2). It was reported that intracerebroventricular infusion of FGF19 improved glucose tolerance^[35] (Figure 2). Interestingly, FGF15-KO mice are glucose-intolerant with <50% hepatic glycogen stored than wild-type mice^[36]. FGF19 can increase hepatic glycogen synthase and glycogen synthesis activity in an insulin-independent manner by inducing the phosphorylation and inactivating the glycogen synthase kinase 3(GSK3)^[36] (Figure 2). Furthermore, FGF19 may also contribute to hepatic glucose homeostasis through its effect on gluconeogenesis.

FGF19 represses gluconeogenesis by inactivating the transcription factor CREB, a key regulator of gluconeogenic genes like peroxisome proliferator-

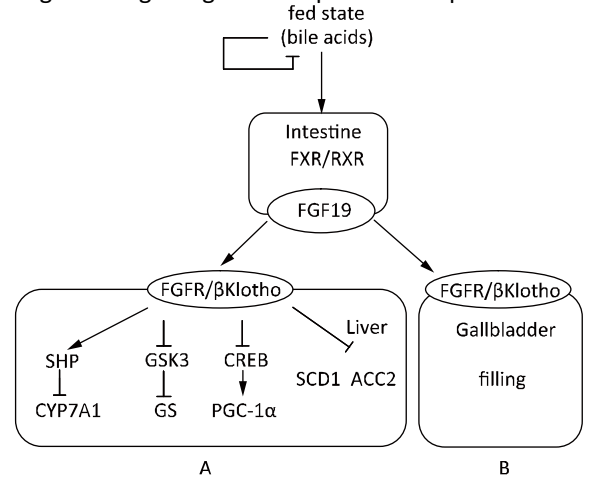


Figure 1. Mechanisms of FGF19 in metabolism. (A) FGF19 expression is induced in the small intestine by bile acids acting on the FXR/RXR heterodimer. Secreted FGF19 acts on FGFR/ β -Klotho receptor complexes in the liver and represses CYP7A1 through SHP, stimulates glycogen synthase (GS) activity and glycogen synthesis through inactivation of glycogen synthase kinase 3 (GSK3), represses gluconeogenesis by inhibiting the activation of CREB, a transcription factor that induces PGC1 α , and increases fatty acid oxidation by repressing SCD1 and ACC2. (B) FGF19 acts on the gallbladder to promote filling of the gallbladder^[33].

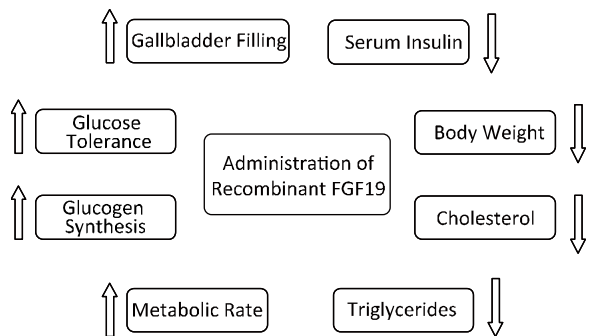


Figure 2. Metabolic effects of FGF19 treatment. Administration of FGF19 caused increase in gallbladder filling, glucose tolerance, glycogen synthesis and metabolic rate, decrease in serum insulin level, body weight, cholesterol level and triglycerides level.

activated receptor g coactivator-1 α (PGC1 α)^[10] (Figure 1).

Lipid Metabolism

Elevated triglycerides and cholesterol levels are the risk factors for cardiovascular disease, diabetes and metabolic syndrome. The weight of FGF19 transgenic mice is less than their wild-type littermates, owing to a decrease in fat content^[34]. Although FGF19 transgenic mice have an elevated food intake, they do not become obese due to enhanced brown adipose tissue (BAT) mass and hepatic lipid oxidation^[34]. Intracerebroventricular infusion of FGF19 reduced 24 h food intake and body weight in male rats^[35]. Similar effects on weight, serum cholesterol and triglycerides levels, and metabolism can be seen in mice fed on high-fat diet after administration of recombinant FGF19^[37] (Figure 2). Several genes are repressed in liver both in FGF19 transgenic mice and in mice treated with recombinant FGF19, including steroyl CoA desaturase-1 (SCD1) and mitochondrial acetyl CoA carboxylase-2 (ACC2)^[34,37]. SCD1 is an essential enzyme involved in the synthesis of monounsaturated fatty acid. ACC2 converts acetyl CoA to malonyl CoA which inhibits carnitine palmitoyl transferase 1 (CPT1) transport of fatty acids into the mitochondria for oxidation. Thus, a reduction in ACC2 activity leads to an increase in fatty acid oxidation (Figure 1). Just like FGF19 transgenic mice, SCD1-/- and ACC2-/- mice are refractory to the effects of a high fat diet on weight gain^[38-39]. However, direct evidence of increased fatty acid oxidation is needed.

CLINICAL CORRELATION

FGF19 and Bile Acid Diarrhea

Enterohepatic circulation plays an essential role in metabolism of bile acids, secretion of bile acids from liver to intestine and reabsorption from the terminal ileum back to the liver^[40]. Bile acid diarrhea (BAD) is a syndrome of chronic diarrhea with excessive colonic bile acids^[41]. Its diagnosis with selenium homocholeic acid taurine (SeHCAT) testing has been validated but is not available everywhere. BAD is classified into 3 types^[42]. The most common form is type I BAD due to ileal dysfunctions^[43]. Type II BAD occurs due to overproduction of bile acids with relatively normal ileum^[44]. Type III BAD characterized by miscellaneous conditions is not

associated with ileal dysfunctions^[42]. It was reported that the defective ileal transport of bile acids leads to a low concentration of bile acids in ileal enterocytes, and FGF19 secretion is reduced in patients with ileal dysfunctions. As decreased FGF19 synthesis from the small intestine results in an impaired feedback inhibition of CYP7A1 in the liver, excess bile acids produced in the liver and secreted into the ileum exceed the reabsorption capacity of the ileum, and excessive colonic bile acids thus produce diarrhea^[45-46]. Ileal bile acid transport is unimpaired in patients with Type II BAD. FGF19 release from the ileal enterocytes is impaired for unknown reasons, resulting in increased hepatic bile acid biosynthesis that in turn causes diarrhea^[45-46]. It has been shown that the median FGF19 level was significantly lower in patients with chronic diarrhea than in normal subjects, and abnormal FGF19 levels are observed throughout the day in some patients with BAD^[46-47], indicating that low serum FGF19 level may be a diagnostic marker of BAD^[46] and FGF19 can be used in treatment of diseases associated with excess bile acids.

FGF19 and Metabolism

FGF19 could also be used in treatment of diabetes and metabolic disorders. It was reported that the serum FGF19 level is related with the serum levels of glucose, HDL-C, and triacylglycerols^[48]. The serum FGF19 level is 65% lower in metabolic syndrome patients than in healthy subjects, indicating that serum FGF19 level is an independent marker of metabolic syndrome^[48]. It has been shown that the serum FGF19 level is negatively related with cardiovascular risk factors such as triglyceride (TG), TG/HDL-C, hs-CRP, and HbA1c in diabetic patients with metabolic syndrome^[49]. A recent study showed that the serum FGF19 level is related with parameters of glucose metabolism in Chinese subjects with normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and newly diagnosed T2DM, demonstrating that the lower fasting serum FGF19 level is negatively related with the fasting plasma glucose level in patients with IFG and T2DM^[50]. In addition, the fasting FGF19 level is significantly lower in obese subjects than in controls^[51]. Wang D et al. reported that the circulating FGF19 level is significantly lower in patients with gestational diabetes mellitus patients than in healthy pregnant women, and the serum FGF19 level is independently and inversely related with the insulin

resistance^[52].

It was reported that the serum FGF19 level is lower in obese adolescents with non-alcoholic fatty liver disease (NAFLD) than in normal subjects, and is inversely associated with the probability of non-alcoholic steatohepatitis and fibrosis in children with NAFLD^[53-55], indicating that low serum FGF19 level is an important risk factor for NAFLD.

Just like insulin, FGF19 can decrease the serum glucose level. However, insulin is secreted within minutes after a meal while the serum FGF19 level reaches its peak 2 h after meal^[9]. In brief, insulin and FGF19 coordinate in a post-prandial hormonal program to adjust nutrient metabolism. Its mechanism still remains unclear so far.

FGF19 and Coronary Artery Disease

The association between FGF19 and the severity of coronary artery disease (CAD) has been investigated in a Chinese population^[56]. The serum FGF19 level is lower in CAD patients than in normal controls and negatively related with Gensini score which can assess the severity of CAD. After adjustment for other CAD risk factors, FGF19 can be considered as an independent factor for Gensini score and the severity of CAD^[56].

FGF19 and Renal Function

FGF19 is a novel metabolic regulator of diabetes mellitus, hyperlipidemia, and adiposity. It was reported in 2010 that FGF19 is related with the renal function in patients on chronic hemodialysis^[57]. The median serum FGF19 level is 1.5-fold higher in patients on chronic hemodialysis than in normal controls, and the circulating FGF19 level is significantly higher in patients with end-stage renal disease than in normal controls^[57]. The circulating FGF19 level is negatively related with CRP in patients on chronic hemodialysis and FGF19 was related with a beneficial metabolic profile both in controls and in patients on chronic hemodialysis^[57]. Further studies are needed to show the effect of FGF19 on renal function in humans.

FGF19 and Cancer

Exogenous FGF19 promotes the growth, invasion, adhesion, and colony formation of prostate cancer cells at a low ligand concentration. FGF19 silencing in prostate cancer cells expressing autocrine FGF19 decreases invasion and proliferation of prostate cancer cells *in vitro* and

tumor growth *in vivo*^[58]. It has been shown that FGF19 is amplified and overexpressed in human hepatocellular carcinoma (HCC), and a neutralizing antibody to FGF19 can block the growth of human HCC cell line^[59]. The expression level of FGF19 is significantly higher in HCC tissues than in corresponding noncancerous liver tissues. FGF19 recombinant protein increases the proliferation and invasion of human HCC. The postoperative serum FGF19 level was lower than the preoperative serum FGF19 level in HCC patients^[60]. It was reported that FGF19 expression is related with tumor size^[61-62].

CONCLUSION

While FGF19 can circulate as a hormone, emerging evidence has showed its autocrine or exocrine function. FGF19 exerts its beneficial effects on carbohydrate and lipid metabolism, and can thus be used in treatment of metabolic disease. However, further study is needed to show the relation of FGF19 with cancer.

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#Correspondence should be addressed to FANG Qi Chen, MD, Tel: 86-21-24058657, Fax: 86-21-64368031, E-mail: qcfang@sju.edu.cn

Biographical note of the first author: ZHANG Jing, female, born in 1989, MD, majoring in diabetes and obesity, E-mail: zhangjing1012@outlook.com

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