Fibroblast growth factor signaling in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: Paving the way to hepatocellular carcinoma

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Abstract

Metabolic disorders are increasingly leading to non-alcoholic fatty liver disease, subsequent steatohepatitis, cirrhosis and hepatocellular carcinoma. Fibroblast growth factors and their receptors play an important role in maintaining metabolic homeostasis also in the liver and disorders in signaling have been identified to contribute to those pathophysiologic conditions leading to hepatic lipid accumulation and chronic inflammation. While specific and well tolerated inhibitors of fibroblast growth factor receptor activity are currently developed for (non-liver) cancer therapy, treatment of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis is still limited. Fibroblast growth factor-mimicking or restoring approaches have recently evolved as a novel therapeutic option and the impact of such interactions with the fibroblast growth factor receptor signaling network during non-alcoholic fatty liver disease/non-alcoholic steatohepatitis development is reviewed here.

Key words: Fibroblast growth factor; Fibroblast growth factor receptor; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Fibrosis; Cirrhosis; Hepatocellular carcinoma

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Core tip: Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis show globally rising incidences and are expected to become the main reason for liver fibrosis, cirrhosis, liver cancer and end-stage liver disease with need for transplantation. Liver metabolism is, among other factors, regulated by fibroblast growth factors and their receptors. This review highlights the role of these signaling pathways in the context of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis and discusses novel treatment options for these otherwise difficult to treat diseases.
INTRODUCTION

Primary liver cancer, hepatocellular carcinoma (HCC) is among the most common cancer related deaths for men and women. HCC commonly develops on the background of various underlying chronic liver diseases and is often called “a disease within a disease”. Besides chronic viral infections and despite the success of vaccination campaigns, its incidence is continuously high, and even increasing, also due to the globally steep increase in metabolic liver diseases leading to non-alcoholic fatty liver disease (NAFLD) and subsequently non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and cancer formation[1,2]. With a global prevalence of about 25%, NAFLD and NASH are a major medical burden and linked to an increasing number of patients with end-stage liver disease and transplantation need. A further increase is expected due to growing prevalence of obesity and metabolic syndrome[3].

The pathophysiologic mechanisms underlying these processes are still not completely clear. Yet, growth factors like the fibroblast growth factor (FGF) family and fibroblast growth factor receptors (FGFRs) can contribute and drive several of these changes and have been clearly shown to possess oncogenic potential in some circumstances[4,5]. In the liver, esp. FGF19, FGF21 and FGF23 have been shown to physiologically possess endocrine functions in regulating, e.g., homeostasis of bile acids and glucose as well as regulating fasting response, lipid metabolism and other conditions[6-10]. As the dysregulation of these metabolic pathways is considered a key feature of chronic liver diseases leading to obesity, metabolic syndrome, NAFLD, NASH, fibrosis and finally HCC, FGFs and FGFRs could be interesting novel targets for diagnosis, surveillance and treatment of these conditions.

PHYSIOLOGY OF FGFRS AND FGFS IN THE LIVER

All four FGFRs are transmembrane tyrosine kinase receptors with a single-pass transmembrane domain, an intracellular kinase domain and three extracellular immunoglobulin-like domains which are subject to alternative splicing and thus mediate ligand specificity. Binding of FGFs leads to receptor dimerization and activation of the downstream signaling cascade that mediates processes linked to cellular survival, extracellular matrix and adhesion molecule signaling but also metabolic processes, e.g., via the PI3K/AKT pathway[11,12]. While the expression of FGFR1 (predominantly mesenchymal tissues) and FGFR2 (predominantly mesenchymal and epithelial) is broad, FGFR3 is mostly found in the central nervous system, bone, skin, and to a lesser extend GI tract, kidney and male and female reproductive tissues. FGFR4 is found in endodermal tissues and the somatic myotome, including endocrine, bone marrow, pancreas, lung and liver and gallbladder tissues[5,13]. In summary, all FGFRs are expressed in the liver with higher levels of FGFR3 and FGFR4[14].

In humans, 22 FGFs have been described so far. They can be subclustered into four intracrine (FGF11-14), fifteen paracrine (FGF1-10, 16-18, 20, 22) and three endocrine (FGF19, 21, 23) subfamilies. They consist of 150-300 amino acids and share about 30%-60% sequence homology with different N- and C-terminal parts mediating receptor specificity. Endocrine FGFs need co-receptors of the Klotho family to bind to any of the four FGFRs. Unlike paracrine FGFs, they lack the heparan sulphate binding capacity and can therefore enter circulation and act as hormones[4,15-17]. The general metabolic functions of endocrine FGFs are reviewed elsewhere[4,18] and we will here focus on their role in physiology and pathophysiology of the liver.

FGF1 is expressed in the liver and other tissues, including adipose tissue where it is upregulated upon high-fat diets[19]. It can bind to all FGFRs and can interact with integrins which are mediators of fibrogenesis, too[20,21]. FGF1 and FGF2 are upregulated in chronic liver disease, fibrogenesis and in HCC where these ligands enhance angiogenesis and invasiveness[22-24]. In addition, FGF1 and FGF2 mediate fibrogenesis by activation of hepatic stellate cells which links extracellular matrix
modulation and carcinogenesis to NAFLD/NASH\[^{22-24}\]. Paracrine FGF8 and FGF10 have been shown to play important roles during embryonic liver development and during liver regeneration\[^{25,26}\]. Esp. FGF10 was shown to regulate hepatoblast function, which links development and repair processes\[^{27}\]. Upon hepatocyte injury, FGF7 induces progenitor cell proliferation in the liver\[^{28}\]. The activation of hepatic stellate cells as a response to injury was linked to FGF9, which also induces hepatocyte proliferation in acute liver injury models\[^{29}\]. Importantly, the activation of hepatic stellate cells as well as the induction of hepatocyte proliferation and recruitment of progenitor cells are key features of acute and chronic liver injury leading to fibrosis, cirrhosis and cancer formation, indicating a central role for FGFs during this process. In human HCC, upregulation of FGF8 family members (FGF8, FGF17 and FGF18) was linked to angiogenesis and enhanced cancer cell survival in 59% of the examined tissue samples. Interestingly, also different FGFRs were upregulated and overall, 82% of cases showed alterations of at least one FGFR and/or FGF\[^{30}\].

Endocrine FGFs have been shown to control several metabolic pathways in the liver via β-Klotho co-signaling. FGF19 (also called FGF15/19 due to its mouse homologue FGF15 which does not exist in humans) is a key regulator of bile acid metabolism and in particular regulation of bile acid homeostasis. The nuclear bile acid receptor FXR induces expression of FGF19 in the ileum which in turn reduces expression of CYP7A1, the rate limiting enzyme for bile acid synthesis in hepatocytes\[^{31}\]. FGF19 was also shown to control gallbladder volume\[^{32}\]. Furthermore, FGF19 stimulates protein and glycogen synthesis in hepatocytes independent of insulin and is thus also involved in glucose homeostasis\[^{33}\].

FGF21 controls a plethora of metabolic pathways in hepatocytes, adipocytes and skeletal muscle\[^{34}\]. Nutritional stress (e.g., low carbohydrate, high fat ketogenic diets) as well as other means of hepatic injury have confirmed FGF21 as a stress response gene in the liver, e.g., by inducing systemic glucocorticoid levels\[^{35}\]. Interestingly, FGF21 was also identified to be a key mediator of metabolic effects mediated by gut microbiota. Several studies recently demonstrated a protective effect of probiotic microbiosa like Lactobacillus species (esp. L. rhamnosus GG) on energy expenditure, dyslipidemia or steatosis in different animal models, which was shown to be dependent on FGF21 signaling and able to reverse NAFLD\[^{36-39}\].

Although FGF23 is linked to calcium and phosphate homeostasis in bone and kidney via α-Klotho co-signaling and not considered to play an important role in liver pathophysiology\[^{40}\], a recent study showed that serum FGF23 was correlated with NAFLD in Chinese patients with type 2 diabetes\[^{41}\]. Although the exact role of FGF23 in NAFLD pathogenesis is unclear, FGF23 mRNA was detected in the liver and is increased under metabolic stress conditions and chronic liver disease in mice\[^{42}\]. Yet the observed increase could also be due to the renal pathophysiology of these conditions\[^{43}\].

**FGF SIGNALING IN NAFLD AND NASH ASSOCIATED LIVER INJURY**

Deployment of extracellular matrix material, fibrosis, is the general response of the liver to chronic injury with hepatocyte damage - independent of the causing agent (viral, toxic, metabolic). Chronic hepatocyte damage and cell death leads to persistent inflammation and activation of wound healing and tissue remodeling programs to compensate the loss of functional hepatocytes and to restrict the damaged area by activation of hepatic stellate cells (Figure 1 and Table 1, for more details on general fibrosis mechanisms in the liver please see\[^{44-46}\]).

Various factors have been described to contribute to NAFLD/NASH and fibrosis progression, like ROS production or inflammatory cytokine release from adipocytes but also impairment of metabolic pathways in the gut and liver like lipogenesis, cholesterol and insulin signaling\[^{47}\]. Dietary factors can influence these pathways and esp. high dietary cholesterol, polyunsaturated fatty acids and fructose have been demonstrated to trigger NAFLD/NASH development\[^{48,49}\]. In absence of insulin, fructose is subjected to liponeogenesis and thus depletes hepatocellular ATP and contributes to mitochondrial damage, ROS production and lipid accumulation, as evidenced by patients with high fructose intake (e.g., soft drinks)\[^{50}\].

Lipid metabolism is considered a key pathogenetic driver of NAFLD progression and fibrosis development. It depends on lipolysis, liponeogenesis and triglyceride oxidation and the overload of the liver with such metabolites can trigger ER stress and autophagy responses\[^{51-53}\].

FGF21 plays a central role here. It is abundantly expressed at low levels in the liver and can be induced upon fasting\[^{54}\] and seems to inhibit lipolysis under this
FGF19 (and its murine homologue FGF15) regulates hepatocyte proliferation. In knockout mice, liver regeneration after partial hepatectomy is impaired and toxic stimuli lead to extensive necrosis and fibrosis, the latter mediated via activation of CTGF signaling[22-24]. In human NAFLD, hepatic response to FGF15 was significantly impaired, esp. under conditions of insulin resistance, and may contribute to lipid and bile acid dysbalance in these patients[54-56]. FGF19 serum levels are reduced in pediatric NAFLD/NASH[74-76]. Upon hepatic injury, FGF21 serves as a protective stress-response regulator and has been shown to ameliorate various hepatoxic conditions (viral hepatitis, alcohol)[69].

Although high levels of FGF21 are considered to be protective against metabolic stress conditions several studies in mice and humans demonstrated also opposite effects. Deficiencies in FGF21 signaling promote HCC growth in mice on long-term obese diet and restoration of FGF21 improves hepatic steatosis[61,62]. In obese humans, increased hepatic FGF21 was described[80] and linked to prevalence and progression of NAFLD, indicating impaired FGF21 function as was seen in type II diabetes with insulin resistance[81]. Elevated expression of FGF21 was also established as a clinical predictive biomarker for steatosis in obese children[82,83] and a panel consisting of FGF21, BMI, γ-GT and triglycerides was proposed as a biomarker for identification of children with steatosis[84]. In adult patients with HIV, elevated FGF21 was confirmed as a risk factor for steatosis[85] and, overall, combined biomarker panels that include FGF21 have higher predictivity for steatosis also in non-obese patients[86]. Interestingly, no data is available on the expression levels of the main receptors for FGF21, FGFR1 and β-Klotho, in NAFLD and NASH.

Maintenance of chronic inflammation is required for the progression of NAFLD to NASH and for fibrosis development. Here, hepatic macrophages, so called Kupffer cells, play a central role in keeping hepatic stellate cells activated. In FGF5 deficient mice, high fat diet lead to severe steatosis and fibrosis via activation of F4/80 macrophages that were positive for CD11b and CD68 and produced TNFα and FasL[80,87].

FGF19 was proposed as a biomarker for steatosis development[73]. In mice, an FGF15-Apo A-I fusion protein (Fibapo) was shown to improve lipid accumulation and metabolic stress under high fat diet conditions in FGF15 knockouts[88], confirming the therapeutic effect of FGF restoration. To overcome potential protumorigenic effects of FGF19 (i.e., induction of cell proliferation), recombinant molecules have been developed and are currently used in human clinical trials. Similar to FGF21, FGF19 was also evaluated as a biomarker for NAFLD and NASH. FGF19 levels were significantly reduced in children with NASH but did not show statistically significant association to the pediatric NAFLD histological score[89]. In a therapeutic study in pediatric patients, FGF19 was significantly increased by lifestyle intervention and a

### Table 1 Role of fibroblast growth factors in non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and hepatocellular carcinoma

| FGFs       | NAFLD/NASH                                                                 | HCC                                                   |
|------------|----------------------------------------------------------------------------|-------------------------------------------------------|
| FGF1       | Upregulated in adipose tissue under high fat diet[9]                        | HSC activation, fibrogenesis, angiogenesis, invasiveness[9] |
| FGF2       | No data                                                                    | HSC activation, fibrogenesis, angiogenesis, invasiveness[9] |
| FGF8 family| No data                                                                    | Proliferation, angiogenesis, matrix modulation[9]     |
| FGF19      | Impaired in NAFLD and by insulin resistance, contributes to lipid and bile acid dysbalance[14-20] | Proliferation, invasion, metastasis, inhibition of apoptosis[10-20] |
| FGF21      | Induced by ketogenic diet, reduces insulin sensitivity, mediator of metabolic effects from gut microbiota[20,21] | Deficiency promotes HCC under obesity conditions[13,21] |

FGF: Fibroblast growth factor; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; HCC: Hepatocellular carcinoma; HSC: Hepatic stellate cell.
Figure 1  Role of fibroblast growth factor signaling in non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and progression to hepatocellular carcinoma. Fibroblast growth factors (FGFs) mediate the key pathogenetic processes linked to development of non-alcoholic fatty liver disease (NAFLD) (metabolic disturbances), non-alcoholic steatohepatitis (NASH) (chronic inflammation) and hepatocellular carcinoma (HCC) (chronic regeneration). FGF21 is mostly involved in mediating metabolic effects during NAFLD and NASH progression, while paracrine FGFs (FGF7, 9, 10) activate hepatocyte proliferation and regeneration processes. FGF19 can inhibit these processes at early stages but may have pro-tumorigenic properties during later disease phases. FGF1, FGF2 and the FGF8 family (FGF8, FGF17, FGF18) mediate HCC formation by supporting angiogenesis, matrix modulation via hepatic stellate cells activation and increasing tumor cell survival. Pointed arrow heads: Activation; Rounded arrow heads: Inhibition. FGF: Fibroblast growth factor; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; HCC: Hepatocellular carcinoma; TG: Triglycerides; FA: Fatty acids; ER: Endoplasmic reticulum; HSC: Hepatic stellate cells.

mix containing docosahexaenoic acid, choline, and vitamin E and was therefore proposed as a pharmacodynamic biomarker in this setting[82]. Overall, the predictivity of FGF19 is still under debate[76].

FGF SIGNALING AS A NOVEL DRUG TARGET IN NAFLD AND NASH

Due to their described hepatoprotective properties and effects on inflammation, metabolism and fibrosis, restoration of FGF19 and FGF21 signaling is considered an attractive novel target for drug development against NAFLD and NASH. In the past, drug development for NAFLD and NASH has been limited by the availability of suitable (surrogate) endpoints and the debate on non-invasive measures is still ongoing[83]. While non-invasive measurements of NASH status and fibrosis have evolved as acceptable endpoints in early stage trials, Phase 3 studies may still require pre- and post-treatment biopsies. Recently, advances in patient selection were achieved that do allow timely readout of e.g., changes in fibrosis, as overall survival may not be achievable pre-cirrhotic patients[53,84].

While several agents are currently in Phase 2 and Phase 3 clinical development for treatment of NASH[83], only few compounds are using FGF signaling as a therapeutic target.

Pegbelfermin (BMS-986036) is a recombinant PEGylated analog of human FGF21. In preclinical models, it improved diabetes, NASH and fibrosis, as demonstrated by increases in adiponectin, improved NAFLD activity score and decreased N-terminal type III collagen propeptide (Pro-C3)[85]. In a Phase 2 study in patients with obesity and type 2 diabetes, pegbelfermin achieved a significant increase in adiponectin and decrease in serum Pro-C3 after 12 wk, comparable to preclinical data. Although effects
on HbA1c were not different to placebo, the drug was overall well tolerated and it was concluded that effects on obesity-related diseases like NASH warrant further investigations[8]. This was further analyzed in a randomized, double-blind, placebo-controlled Phase 2 study in patients with confirmed NASH, fibrosis and obesity. Pegbelfermin was administered subcutaneous in a daily (10 mg/d) or a weekly (20 mg/wk) schedule for 16 wk and primary endpoints were changes in magnetic resonance imaging proton density fat fraction (MRI-PDFF), serum Pro-C3, transaminases, and liver stiffness as assessed by MR elastography. A total of 74 patients were enrolled and 68 were eligible after 16 wk of treatment. Here, a significant reduction in MRI-PDFF (-6.8% and -5.2%, respectively) and transaminases (-33.0% and -23.7% for alanine aminotransferase, -30.9% and -26.2% for aspartate aminotransferase, respectively) was detected in both treatment schedules. Furthermore, a significant proportion of patients showed improved serum Pro-C3 and reduced MR elastography liver stiffness, all paralleled by an approximate 15% increase in adiponectin versus placebo. Overall, the drug was also well tolerated in these patients and results from this study suggest clearly a beneficial effect on steatosis, liver injury and fibrosis in NASH patients[8]. Currently, additional studies are ongoing to evaluate pegbelfermin in patients with NASH associated fibrosis, cirrhosis or impaired kidney function.

NGM282 is a recombinant non-tumorigenic variant of FGF19. It was modified at the amino-terminal end to bind to FGFR4/β-Klotho, suppress CYP7A1 expression (the rate limiting step in bile acid synthesis) but does not activate STAT3 signaling which is considered a main driver for hepatocarcinogenensis[10]. Preclinically, NGM282 improved inflammation, hepatocyte damage and fibrosis in models of NASH and of sclerosing cholangitis in mdr2-deficient mice[99,98]. It was well tolerated also in humans and showed signs of reduced CYP7A1 activity, too[94,90]. In a randomized and placebo-controlled Phase 2 study, NGM282 lead to a rapid reduction in hepatic fat content in more than 70% of the treated patients after 12 wk, paralleled by significant reductions in transaminase and Pro-C3 levels and ELF fibrosis score and increase in low density lipoprotein cholesterol. The overall safety profile was acceptable with predominantly Grade 1 adverse events. As NGM282 is a recombinant peptide, anti-drug antibodies were observed in a small number of patients but were considered not to be neutralizing[92,91]. After 12 wk, NAFLD activity score was dose-dependently reduced by 2 points in up to 63% of patients without worsening of fibrosis and fibrosis was reduced by one or more stages in up to 42% of patients[94,95]. Due to its effects on CYP7A1, NGM282 increases low density lipoprotein cholesterol and serum cholesterol. Thus, combination with rosuvastatin was assessed to further improve the cardiovascular risk profile for NASH patients[93].

While these approaches focus on ligands, also FGFRs could be a promising target for NAFLD and NASH drug development. Several small molecule kinase inhibitors targeting FGFRs are currently in clinical development for the treatment of various solid tumors. Yet, in none of the early clinical trials with these multi-kinase inhibitors (usually targeting FGFR1-3), metabolic effects related to FGF signaling other than phosphate increase due to renal FGFR1 inhibition were reported. BLU9931 as well as H3B-6527, two specific inhibitors of FGFR4, suppressed HCC growth in preclinical models but also induced expression of CYP7A1, although no adverse effects on lipid metabolism or steatosis were observed in the investigated rodent models[87,92,93,94].

The protective effects of FGF19 via inhibition of endoplasmic reticulum stress, which is commonly observed in metabolic overload during NAFLD and NASH, have been shown to be mediated via the FGFR4/β-Klotho pathway[90]. An upregulation of FGFR4 was recently demonstrated in murine NASH models[94] and in patients developing HCC on fatty liver disease background[95]. To block FGFR4 signaling, a soluble FGFR4 extracellular domain fragment was developed that specifically inhibits FGFR4 activation in vitro and suppressed steatosis and fatty liver development in mice[96], but clinical data in humans is still lacking.

Mimicking FGFR activation is currently investigated with NGM313, a humanized monoclonal antibody binding to an epitope in β-Klotho. It was shown that NGM313 activates FGFR1c signaling, similar to the physiologic role of FGF21. A single dose of NGM313 significantly reduced liver fat content, transaminase levels, HbA1c, triglycerides and low density lipoprotein cholesterol in obese patients with insulin resistance and NAFLD[97].

**FGFS AND FGFRS IN HCC**

The above outlined pathways of chronic inflammation and hepatocyte stress conditions commonly involve FGF signaling and various approaches in restoring FGF
physiologic conditions have been successful in preventing HCC development in preclinical models. In human HCC, several studies confirmed overexpression of different FGFs and FGFRs, which confirms the attractiveness of targeting FGF signaling also in established HCC[102,103]. FGF19 was recently proposed as a novel diagnostic biomarker with better accuracy than AFP for small HCCs[104]. As many FGFs can have different pro-tumorigenic effects (e.g., by promoting angiogenesis or chronic inflammation), FGFRs seem to be the more attractive here. While esp. inhibition of FGF4 was shown to reduce growth of experimental HCC models[105,106] and is considered an attractive drug target[107,108], also FGF1, FGF2 and the FGF8 subfamily as well as targeting FGFR1-3 have been shown to possess preclinical anti-HCC activity[109,110,111]. Designing specific inhibitors for FGFR4 was considered challenging and therefore initial approaches used multi-kinase or pan-FGFR inhibitors. While sorafenib was the first multi-kinase inhibitor to achieve an overall survival benefit in HCC[112], other compounds like brivanib or lenvatinib did not achieve this endpoint[113,114]. Preclinically, the specific FGFR4 inhibitors BLU-9931, H3B-6527 or INC8062079 showed promising activities.

Several clinical studies with these and other FGFR4 specific inhibitors are currently ongoing in HCC patients. Phase 1 data for fisoqatinib (BLU-554) indicate good target engagement and inhibition of FGFR4 as shown by effects on bile acid and cholesterol synthesis pathways in a dose-dependent manner. With an overall good tolerability, the compound showed signs of clinical efficacy in FGF19-positive HCC patients[115]. FGF401 showed an increase in transaminases and induction of CYP7A1 in preclinical toxicology studies and co-administration of cholestyramine improved the safety profile here[116]. In humans, increase in transaminases was seen, too, but the overall safety profile is considered acceptable and no maximum tolerated dose was reached in a Phase 1/2 study. Patients had to be positive for FGFR4 and β-Klotho expression to be eligible to participation and the overall response rate in the Phase 1 population was about 8%[116].

CONCLUSION

The high global prevalence of NAFLD and NASH warrants the search for novel treatment options. FGF signaling mediates central metabolic effects in the liver (and other tissues) that are directly linked to the overload of hepatocytes with toxic metabolites and pathogenesis of lipid accumulation and chronic inflammation leading. Several approaches, e.g., FGF-mimicking peptides or receptor-specific targeting agents, have shown promising signs in preclinical and early clinical studies in humans. Yet, due to the plethora of ligands and receptors and a high tissue context dependency, further studies and esp. also long-term studies are urgently needed to fully understand how FGF and FGFR signaling pathways can be fully exploited for the benefit of affected patients.

Specific FGFR4 inhibitors are currently tested in clinical trials in HCC. The positive preclinical results are reflected in encouraging early clinical data from different Phase 1 studies. Yet, the overall efficacy of these compounds needs to be carefully investigated compared to current multi-kinase inhibitors and the emerging immune checkpoint inhibitors.

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