The role of fibroblast growth factor 21 in the pathogenesis of liver disease: a novel predictor and therapeutic target

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Introduction: Fibroblast growth factor 21 (FGF21) is one of the FGF family members that is produced mainly by tissues with high metabolic activity such as liver, pancreas, muscle and adipose tissue. The major function of FGF21 is to improve insulin sensitivity, ameliorate hepatic steatosis and enhance energy expenditure. Recently, several studies have reported a correlation between FGF21 and liver disease with numerous cross-sectional studies demonstrating significant correlation. This review will focus on the role of FGF21 in the pathogenesis of liver disease and its potential role as a biomarker and a new target for therapeutic intervention.

Areas covered: This review discusses cross-sectional studies and underlying mechanisms of FGF21 as an endocrine hormone in several liver diseases. Two major theories of ‘endoplasmic reticulum stress’ and ‘FGF21 resistance’ in particular are explained. Moreover, early functional detection and pharmacological effect of FGF21 for liver disease are also described.

Expert opinion: FGF21 can be a promising treatment in liver disease. However, still several problems are needed to be answered. The most important are whether different liver disease share common underlying mechanisms and the pharmacological effect in human with limited studies. Further studies are needed to explain the underlying mechanisms and develop potential therapeutic effect for human liver disease.

Keywords: alcoholic liver disease, endoplasmic reticulum stress, fibroblast growth factor 21 resistance, fibroblast growth factor 21, hepatocellular carcinoma, nonalcoholic fatty liver disease, pathogenesis, therapeutic target, viral hepatitis

1. Introduction

Fibroblast growth factor 21 (FGF21), a metabolic hormone expressed in multiple peripheral tissues, such as liver, muscle, pancreas, brown adipose tissue (BAT) and white adipose tissue [1-5], was first identified in mouse embryos by homology-based polymerase chain reaction in 2000 [3]. Unlike other FGFs, FGF21 lacks a heparin-binding domain and travels through the circulation acting as a hormone exerting multiple metabolic effects, such as glucose and lipid control, insulin sensitivity and energy homeostasis in experiment animal models of metabolic syndromes [6,7]. Investigation of the underlying mechanisms of FGF21 function and the potential usage as a biomarker and as a pharmacological agent for the treatment of metabolic disease has received increasing attention. Recently, studies have provided evidence that one of the major target tissues of FGF21 action is likely adipose tissue [8,9] and that secreted FGF21 may be a beneficial factor in adipose tissue biology.

10.1517/14728222.2014.944898 © 2014 Informa UK, Ltd. ISSN 1472-8222, e-ISSN 1744-7631
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through a single-pass membrane-spanning protein β-Klotho with the associated FGF receptor tyrosine kinase [10].

Previous studies have shown that elevated FGF21 secretion may be an adaptive response to starvation and fasting [11], and more recently, researchers have found that FGF21 expression is correlated with liver diseases, such as steatosis, viral infection and carcinogenesis [12-14]. The role of FGF21 in hepatic lipid metabolism has been attributed to improvement of adipocyte lipolysis and fatty acid oxidation, and up-regulation of the adipokine-adiponectin expression to reduce the liver’s steatotic burden [15]. Although the complexity of understanding individual patient effects and mechanisms in each liver disease require more study, secreted FGF21 appears to show some benefit in improving insulin sensitivity and in the attenuation of hepatic steatosis (Figure 1) [16,17].

2. FGF21 in alcoholic liver disease

Alcoholic liver disease (ALD) presents as a broad range of liver disorders, including alcoholic fatty liver, alcoholic hepatitis, fibrosis and cirrhosis, which may eventually lead to hepatocellular carcinoma (HCC). The incidence of alcohol-induced liver injury has significantly increased over recent years and is becoming a primary cause of chronic liver disease worldwide. In the US, up to 48% of deaths are due to alcohol-induced liver injury, a major contributor to mortality [18]. Unfortunately, an exact knowledge of the pathogenesis of ALD is lacking to date and no drug has emerged as an effective therapy for ALD. Alcohol consumption not only disrupts fatty acid β-oxidation but also stimulates fatty acid synthesis in hepatocytes. Hepatic steatosis is the earliest response to alcohol consumption, which further develops to more severe forms of alcoholic liver injury. Additionally, adiposity had been shown to be another important risk factor for ALD, which may accelerate the progression of fibrosis and cirrhosis and lead to the development of advanced ALD [19,20]. Thus, the main clinical objective in the treatment of ALD is to improve lipid disturbance and prevent the progression of hepatic steatosis.

Previous studies have indicated that alcohol consumption may inhibit PPAR-α activity in the hepatocyte [18,21,22], leading to the inhibition of fatty acid oxidation. Unexpectedly, recent studies also showed that there was a highly significant association between PPAR-α and FGF21 expression in the liver [23-25] and FGF21 has been identified as a mediator of the activity of PPAR-α [24]. Moreover, FGF21 can be induced directly by PPAR-α in the liver in response to fasting and mediate hepatic lipid metabolism [26], supporting the role of the PPAR-α and FGF21 endocrine signaling pathway in this organ. FGF21 was shown to have a significant effect on improvement of lipoprotein profiles, where it lowered low-density lipoprotein cholesterol and increased high-density lipoprotein cholesterol, thus implicating the potential contribution of FGF21 on lipid metabolism [23,27,28]. Furthermore, in diet-induced obese (DIO) mice, FGF21-treated, but not vehicle-treated animals showed hepatocellular vacuolation and intense oil-red-O-stained lipid [12]. Biochemical analysis also showed marked reductions of hepatic triglyceride and cholesterol content in livers of FGF21-treated, but not vehicle-treated DIO mice, and this observation has been confirmed in a subsequent study [29]. It appears that FGF21 may correct multiple metabolic disorders and reverse hepatic steatosis in DIO mice. Therefore, it may appear a reasonable hypothesis that FGF21 could have an effect on the prevention of ALD by modulating the lipid metabolic profile at the early stage of the disease.

Recently, a study indicated serum levels of FGF21 were markedly increased in ALD, involving both acute alcoholic hepatitis human subjects and chronic-binge animal models [30]. In animal models, mice were fed chronic and acute binge dose of ethanol, which induced higher levels of steatosis in ALD [31]. Thus, this study appears to validate our assumption that FGF21 may play a crucial role in steatosis. In addition, alcohol exposure was demonstrated to upregulate FGF21 by decreasing the expression of peroxisome proliferator activated receptor co-activator-1α and Rev-Erbα, which are transcriptional suppressors of FGF21. However, the elevated expression of FGF21 appeared contradictory with the inhibition of PPAR-α according to the aforementioned positive association between them. Therefore, at this stage, further biochemical investigation is required to reveal the underlying mechanism in ALD.

3. FGF21 in nonalcoholic fatty liver disease

The prevalence of nonalcoholic fatty liver disease (NAFLD) has rapidly increased in recent years and has become one of the most common chronic liver diseases worldwide [32]. Currently, it is recognized as one of the components of metabolic syndrome in addition to obesity and insulin resistance [33]. The pathological changes of NAFLD comprise a chronic process ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis/cirrhosis and even HCC. It is becoming increasingly evident that early diagnosis and intervention for disease are crucial [34]. NAFLD, in particular NASH, had been identified as an independent risk factor for malignancy, ischemic heart disease and liver-related complications [35,36]. As a result, patients with NAFLD have elevated prevalence of mortality and morbidity [37,38].

At present, several nuclear receptors (NRs), transcription factors and other proteins have been linked with NAFLD...
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**Figure 1. The endocrine signaling pathway of FGF21.** FGF21 is expressed by the liver, muscle, pancreas, BAT and WAT. Unlike other FGFs, FGF21 lacks a heparin-binding domain and travels through the circulation. The major target tissues of FGF21 are adipose tissues through a single-pass membrane-spanning protein β-Klotho (KLB) with FGF receptor tyrosine kinases (FGFR). Two common effects were reported in liver injuries with FGF21 to improve insulin sensitivity, clearance of systemic lipids and attenuate hepatic steatosis. First, FGF21 improves adipocyte lipolysis and fatty acid oxidation. Secondly, FGF21 upregulates adipokine adiponectin in order to reduce the liver’s steatotic burden indirectly.

**BAT:** Brown adipose tissue; FGF21: Fibroblast growth factor 21; WAT: White adipose tissue.

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FGF21 is a protein and a non-coding RNA molecule that are involved in stress responses. FGF21 is expressed by the liver, muscle, pancreas, BAT and WAT. Unlike other FGFs, FGF21 lacks a heparin-binding domain and travels through the circulation. The major target tissues of FGF21 are adipose tissues through a single-pass membrane-spanning protein β-Klotho (KLB) with FGF receptor tyrosine kinases (FGFR). Two common effects were reported in liver injuries with FGF21 to improve insulin sensitivity, clearance of systemic lipids and attenuate hepatic steatosis. First, FGF21 improves adipocyte lipolysis and fatty acid oxidation. Secondly, FGF21 upregulates adipokine adiponectin in order to reduce the liver’s steatotic burden indirectly.

**BAT:** Brown adipose tissue; FGF21: Fibroblast growth factor 21; WAT: White adipose tissue.
resistance\(^5\). Although the concept of overt ‘FGF21 resistance’ has been challenged, it remains a testable hypothesis for future studies.

### 4. FGF21 in HCC

HCC is one of the most common cancers worldwide with ill-defined molecular mechanisms and a poor prognosis\(^5\). Recent studies have suggested that FGF21 was over-expressed both in human disease and a murine model\(^14,59\). In human HCC, a high level expression of FGF21 protein was demonstrated in grade 1 HCC but not grade 2 and grade 3 tumor cells. This difference may be due to the reserved function of FGF21 secretion in the better differentiated grade 1 cells. Although the underlying mechanism of elevated FGF21 protein in human liver tissues is unclear, researchers discovered a series of genes, which play a crucial role in HCC animal models, that may be associated with FGF21 expression. In the p53 knock-out mouse model, the expression of FGF21 was markedly increased in liver tissues. This may suggest that haplo-insufficiency of p53 could significantly promote FGF21 expression. Furthermore, in vitro using luciferase reporter assays, p53 expression was able to downregulate FGF21 promoter activity via the cis-acting sequence in the proximal promoter of FGF21. Consequently, when dysregulation of p53 protein expression occurs, a large number of FGF21 is activated in liver tissues\(^60\). Recently, a study showed that PPAR-\(\alpha\) participates in hepatocarcinogenesis\(^56\). In this study, researchers described that the sustained PPAR-\(\alpha\) activation induced hepatocellular proliferation. Based on the positive correlation of FGF21 and PPAR-\(\alpha\) aforementioned, this may offer a plausible explanation for the increase of FGF21 in HCC, although the precise involvement of p53 has yet to be determined. As the sustained PPAR-\(\alpha\) activation results in hepatocellular proliferation, it is unlikely that FGF21 directly induces hepatocarcinogenesis, which is in contrast to the role of FGF19\(^61\). Both FGF19 and FGF21, which harbor differences in a 5 amino acid region (residues 38 – 42), play a similar role in metabolism, decreasing body fat mass, improving insulin sensitivity, glucose disposal and plasma lipid parameters\(^12,27,62,63\). This 5 amino acid sequence renders FGF21 unable to activate FGF receptor 4, which increases hepatocyte proliferation and results in HCC. Therefore, upregulated FGF21 appears to act as a beneficial function to lipid metabolism as opposed to direct hepatocyte proliferation and carcinogenesis.

Taken together, data derived from both the murine models and human hepatocyte studies reached the same conclusion that FGF21 was up-regulated in HCC, with FGF21 showing a negative association with p53 in animal models. These findings support a possible underlying regulatory mechanism for FGF21 elevation in animal models and humans with liver damage and carcinogenesis. Moreover, FGF21 expression is also associated with lipid metabolism regulated by several NRs.

### 5. FGF21 in viral hepatitis

Viral hepatitis is one of the major causes of acute and chronic liver disease leading to steatosis, cirrhosis and eventually
HCC [64]. Over 2 billion people worldwide are infected with hepatitis B virus (HBV) and hepatitis C virus (HCV), and ~850,000 people die from hepatic virus infection or its complications each year [65].

HCV infection may correlate with FGF21 expression [13,66]. In HCV infected patients, studies showed that both mRNA levels of PPAR-α and FGF21 were downregulated with a concomitant elevation in the level of HCV RNA [13]. However, in another cross-sectional study, serum FGF21 level suggested a positive correlation with steatosis grade in chronic hepatitis C patients [66]. Given FGF21 elevation in the subjects with hepatic steatosis could induce several liver diseases aforementioned, it is possible that FGF21 is increased in HCV.

At present, the underlying mechanism of HCV disease pathogenesis is unclear; however, FGF21 in HCV has been shown to share some common molecular mechanisms with other liver diseases. The over-expression of HCV non-structural protein 4B (NS4B) could induce ER stress and UPR [67]. NS4B is an ER membrane-associated protein, which is encoded by HCV single-stranded RNA genome [68].

In this study, it was proposed that NS4B could induce the X-box binding protein 1 mRNA splicing and activating transcription factor-6 cleavage resulting in UPR. Therefore, ER stress activation is likely a mechanism by which FGF21 is upregulated in HCV patients.

In contrast to the positive association between FGF21 and HCV, a nonsignificant correlation was reported between FGF21 expression and HBV infection [69].

6. Biomarker and therapeutic effect

Early intervention plays a crucial role in the therapeutic treatment of liver disease. At present, the gold standard for diagnosis and classification of NAFLD and NASH is liver biopsy [70-72]. A liver biopsy has the advantages of revealing the stage of liver steatosis, damage in liver architecture, as well as the severity of fibrosis. However, it is rare and invasive, leading to possible procedural complications such as hemorrhage.

Although high-resolution ultrasound B-mode examination is inexpensive and noninvasive, only a degree of liver steatosis ≥30% can be detected [73]. Therefore, a reliable noninvasive means of early diagnosis for liver disease is needed. Recently, a number of parameters have been demonstrated to be significantly associated with liver disease, such as age, diabetes, increased insulin resistance (Homeostasis Model Assessment [HOMA]), aspartate transaminase/alanine transaminase ratio, platelet count, body mass index (BMI) and hyaluronic acid [74].

FGF21 has also been suggested to be a biomarker, which could predict and differentiate liver disease. In a prospective cohort study, baseline FGF21 level and BMI were described as independent predictors for NAFLD development (named as FGF21 Model) [41]. Moreover, the receiver operator curves representing the predictive accuracy of the FGF21 Model for NAFLD have been calculated. The performance of the FGF21 Model was better than that of FGF21 alone and a similar conclusion also had been reached in an independent study [42]. In addition to this finding, FGF21 mRNA expression was elevated followed by the severity of steatosis in NAFLD [45]. This result may suggest that FGF21 could not only predict NAFLD development but also classify the grades of steatosis. In addition, patients in clinical conditions of HCV and hepatocarcinogenesis may also be diagnosed through detection of FGF21 protein [13,14].

Although FGF21 may act as an important biomarker for several liver diseases, it may also have potential as a therapeutic agent for disease. As described above, FGF21 administration has shown beneficial effects in lipid metabolism, and decrease in lipid parameters and alteration of gene expression for those involved in lipid metabolism have been reported in diabetic and obese rodents by systemic administration of FGF21 [27]. In addition to showing effects on lipid levels in the liver, attenuated lipid accumulation was revealed in muscle and BAT in FGF21-treated DIO mice. FGF21 also has a beneficial effect in weight loss in primates [28]. As obesity is an independent risk factor associated with NAFLD [75-77], FGF21 may play a pivotal role in NAFLD therapy. A study conducted in a murine model of insulin resistance suggested that FGF21 markedly reduced body weight, improved insulin resistance and attenuated hepatic steatosis in NAFLD [78]. These findings add support to the potential of a therapeutic effect of FGF21 in NAFLD as a novel therapy for clinical application. However, to date, no pharmacological intervention study has been performed in patients and so the feasibility of conducting a clinical study in a defined patient group may warrant attention of the scientific community.

7. Conclusion

Over-expression of FGF21 protein has been observed in a variety of liver diseases, such as ALD, NAFLD, HCC and viral hepatitis. Elevated FGF21 mirrors lipid accumulation in hepatocytes regulated by PPAR-α pathway. Once elevated, FGF21 shows a protective effect in liver disease, which includes an improved clearance of systemic lipids and enhanced insulin sensitivity. The underlying molecular mechanisms responsible for disease progression are not completely understood. At present, the most likely credible explanation is that increased expression of FGF21 is induced by liver stress, as ER stress. Induced FGF21 expression is likely a biomarker for early detection for liver injury. Administration of FGF21 has shown therapeutic benefit in rodent and primate models of metabolic diseases.

8. Expert opinion

Although the correlation of FGF21 expression with liver diseases has been described, (Table 1), the precise role of FGF21 in the four major liver diseases discussed remains incompletely understood. As steatosis represents pathology in
the early phase of both ALD and NAFLD, we hypothesize that FGF21 may show a similar dependence through common mechanisms of ALD. Although FGF21 was upregulated in both ALD and NAFLD, the inhibition of PPAR-α in ALD and over-expression of PPAR-α in NAFLD may appear to contradict each other and so the underlying mechanism of FGF21 induction in ALD requires further exploration.

Although ER stress is the most recognized mechanism for NAFLD and similar liver injures, a smaller number of prior studies had described a theory of ‘FGF21 resistance’. It may be questioned whether FGF21 resistance exists and the validity of this assumption remains to be confirmed or refuted.

Similar pathological processes, from steatosis to HCC in liver disease, may implicate common underlying mechanisms between and across these conditions as both PPAR-α attenuation and ER stress have been implicated in several liver diseases. Moreover, other forms of intracellular stress also induce FGF21 expression, as nutrient and oxidative stress, by phosphorylation of eIF2α. So, we hypothesize that each liver disease may act as a kind of liver stress leading to the ER stress-like response and phosphorylation of eIF2α by the PPAR-α pathway, resulting in a change of FGF21 expression. Although there is no evidence to support this molecular mechanism at present, whether increase in the levels of FGF21 protein in different liver disease occurs through the same mechanism requires further study.

Lastly, both acute and chronic liver diseases encompass a spectrum of liver disease that starts with steatosis and progresses to hepatitis, fibrosis, cirrhosis and even HCC. Despite current research exploring the correlation of FGF21 and several liver diseases aforementioned, the individual pathological activity of FGF21 in each stage of liver disease deserved to be further discussed, especially in liver fibrosis and liver failure. Recently, a study involving pediatric NAFLD indicated that FGF21 was inversely associated with the probability of fibrosis (79). We hypothesis that this finding may result from lost functional secretion of FGF21 secretion in late stages of disease. However, relevant clinical data and mechanistic studies are still limited. Therefore, further studies investigating the modulation of FGF21 expression in late stage of liver disease are warranted.

Finally and as with all emerging targets, early research is dedicated to an understanding of the underlying molecular mechanisms, which are based on in vitro or nonclinical animal models. It should be borne in mind that since human FGF21 is a polypeptide of 181 amino acids with 25% different from mouse FGF21 (3), a potential difference in downstream pathologies may result when a therapy targeting FGF21 is tested in the clinic. Although evidence is obtained from protein expression from patients with liver disease, further studies are needed to provide insight into the role of FGF21 in the clinic and our opinion supports the further assessment of this target in liver disease.

### Acknowledgments

This work was supported by grants from the Scientific Research Foundation of Wenzhou, Zhejiang Province, China (H20090014, Y20090269), Health Bureau of Zhejiang Province (2010KYB070), Research Foundation of Education Bureau of Zhejiang Province (Y201009942), Fresh Talent Program for Science and Technology Department of Zhejiang Province (2013R413018, 2013R413035 and 2013R413015), Research Funds for Tian Qing Liver Diseases (TQGB20120057) and Project of New Century 551 Talent Nurturing in Wenzhou.

W-Y Liu, S Huang and K-Q Shi contributed equally to this work.

### Declaration of interest

The authors were supported by the Scientific research foundation of Wenzhou, Health Bureau of Zhejiang Province, Education Bureau of Zhejiang Province, Science and Technology department of Zhejiang province, New Century 551 Talent Nurturing in Wenzhou. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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**Table 1. Questions of the review.**

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<td>Why is PPAR-α inhibited in ALD in contrast to the over-expression in NAFLD?</td>
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<td>Is FGF21 elevated in ALD as well as in NAFLD?</td>
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<td>Does FGF21 resistance really exist in NAFLD and does it lead to the elevation of FGF21?</td>
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<tr>
<td>Does different liver disease share common underlying mechanisms, such as the ER stress and PPAR-α pathway?</td>
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<td>What is the difference of FGF21 in different stage of liver disease?</td>
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<td>What are the differences between human and animal models of FGF21 effects and mechanisms, especially in pharmacological studies?</td>
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**Legend:** ALD: Alcoholic liver disease; ER: Endoplasmic reticulum; FGF21: Fibroblast growth factor 21; NAFLD: Nonalcoholic fatty liver disease.
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