Experimental Cell Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Experimental Cell Research

journal homepage: www.elsevier.com/locate/yexcr

# Fatty liver and FGF21 physiology

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ARTICLE INFO

*Keywords:*
Non-alcoholic fatty liver disease
FGF21
Obesity
Metabolic syndrome
Insulin resistance

ABSTRACT

Non alcoholic fatty liver disease is linked to obesity and the metabolic syndrome. As rates of obesity rise it has become the major etiology of liver dysfunction. Despite intense study the molecular mechanisms contributing to the onset of fatty liver remain debatable. Furthermore, few therapies exist and as a result dietary therapy is commonly prescribed and remains problematic. Fibroblast growth factor is a complex metabolic regulator that is synthesized in multiple organs including the liver, with resulting complex systemic effects. Several lines of evidence suggest that effects in the liver lead to decreased fat accumulation and that treatment results in reduced inflammation and fibrosis. Understanding the physiology of FGF21 is important to the understanding of liver disease and may also provide targets for future therapy.

## 1. Overview of fatty liver disease and metabolic dysfunction

The role of the liver in glucose homeostasis has been recognized for at least a century. Studies in humans examining hepatic insulin sensitivity date back to the early 1950s when it was possible to insert catheters and sample blood flow and compare concentrations of glucose in the hepatic vein and peripheral capillaries. These studies distinguished between normal subjects, lean, type 1 subjects and obese type 2 subjects on the basis of both insulin sensitivity and hepatic lipid accumulation [1]. These studies also described the severe insulin resistance that accompanies diabetic ketoacidosis. Increasingly the role of hepatic fat was noted as a feature of obesity and type II diabetes although as recently as 2001 one of the classic textbooks in endocrinology devoted only part of a chapter on factors that might integrate hepatic liver accumulation with insulin resistance and metabolic syndrome. However, it is noteworthy that in the more than sixty-year interval since the original human studies and hundreds of published manuscripts implicating dozens of potential mediators there is still controversy about the specific role of the liver in metabolic disease and there is still debate as to whether hepatic lipid accumulation precedes or is a cause of disease.

Nonalcoholic fatty liver disease (NAFLD), characterized by excess hepatic accumulation of triglycerides, is a common complication of obesity and is linked to insulin resistance and the metabolic syndrome. Rising rates of obesity in the United States and the world have been accompanied by increased rates of NAFLD, which typically presents as fatty liver but can progress to both steatosis and cirrhosis and hepatocellular carcinoma. As assessed by MRI, a liver with more than 5% fat is considered early steatosis and total liver fat by MRI correlates well with hepatic fat observed on liver biopsy [2]. By histology, hepatosteatosis is diagnosed when 5% of all cells contain lipid droplets [3]. Diagnosis of NAFLD requires exclusion of other causes of liver pathology, including alcohol abuse, viral infections and biliary or autoimmune disease. 10–20% of individuals with NAFL progress to nonalcoholic steatohepatitis (NASH) which is characterized by hepatocyte lipoapoptosis, inflammation and fibrosis. While fatty liver has a relatively benign prognosis [4], NASH poses a high risk for further progression to cirrhosis and hepatocellular carcinoma (HCC). As a result of the increasing prevalence of obesity, NAFLD is now the most common cause of chronic liver disease in developed as well as developing countries. In the USA NAFLD affects 30% of the obese population and 53% of obese children [5,6]. Additionally, risk increases with weight and prevalence increases to 90% in morbidly obese populations [7,8]. Unfortunately, at present it is not possible to identify individuals who will progress from NAFL through NASH to fibrosis and HCC. In addition, effective treatments are limited to weight loss which is problematic as except for bariatric surgery, few interventions lead to meaningful sustained weight loss. Thus, understanding the molecular mechanisms underlying the progression from hepatic steatosis to frank steatohepatitis is of critical importance for clinical assessments and for pharmacological treatment.

While the pathological diagnosis of fatty liver is straightforward the mechanisms that lead to hepatic lipid droplet accumulation in multigenic “common” obesity are complex and poorly understood. One theory implicates saturation of adipose fat stores leading to overflow of triglycerides into other organs including liver, muscle and pancreas. A

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http://dx.doi.org/10.1016/j.yexcr.2017.05.006
Received 1 May 2017; Accepted 4 May 2017