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Emerging roles for stress kinase p38 and stress hormone fibroblast growth factor 21 in NAFLD development

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD), the most frequent cause of chronic liver disease worldwide, is associated with a plethora of metabolic comorbidities such as obesity, prediabetes, type 2 diabetes mellitus, hypertension and dyslipidemia but may be present in a significant percentage of non-obese subjects. Recent evidence has highlighted that NAFLD is characterized by the dysregulation of hepatokines, including fibroblast growth factor 21 (FGF21). "FGF21 resistance" observed in obesity and NAFLD is actually not fully understood. A very recent study by Hao Ying et al. in *Diabetes* provides new insight into the roles of hepatic stress kinase p38 and FGF21 in the pathogenesis of NAFLD. This study has shown that mechanistically, via the elevation of hepatic FGF21, p38α activation increases the influx of fatty acids from the adipose tissue to liver, resulting in hepatic ectopic lipid accumulation and insulin resistance. Despite the favorable effects of p38α activation on peripheral tissues, it may impair the hepatic FGF21 properties by enhancing the degradation of FGF21 receptor cofactor β-Klotho. In the fatty liver of either mice or patients, the study has shown that p38α phosphorylation and FGF21 expression were elevated while β-Klotho protein levels were diminished. Based on the observation that mice with hepatic p38α activation exhibit not only hepatic steatosis but also reduced adiposity, which is similar to those observed in lean NAFLD, these findings may also provide a plausible explanation for the lean phenotype seen in NAFLD. In conclusion, this study highlighted previously undescribed effects of hepatic p38 activation on systemic metabolic homeostasis providing novel insights into the contribution of hepatic p38α, FGF21, and β-Klotho in the etiopathogenesis of NAFLD.

Non-alcoholic fatty liver disease (NAFLD), which is currently the most frequent cause of chronic liver disease worldwide, is characterized by the accumulation of fat in the liver (steatosis) exceeding 5% of total liver's weight, in the absence of significant alcohol consumption [1–3]. NAFLD is associated with a plethora of metabolic comorbidities such as overweight/obesity, prediabetes, type 2 diabetes mellitus (t2DM), hypertension and dyslipidemia [1–4]. NAFLD could also be present in a significant percentage of non-obese subjects [1]. Liver is considered an endocrine organ that modulated systemic lipid homeostasis via the production of hepatokines [5]. Recent evidence has highlighted that NAFLD is characterized by the dysregulation of hepatokines [5]. Fibroblast growth factor 21 (FGF21) is a hepatokine targeting mainly the white adipose tissue and exhibiting favorable actions in hepatic lipid metabolism and insulin sensitivity [6]. Interestingly, elevated levels of FGF21 and "FGF21 resistance" have been associated with obesity, insulin resistance, t2DM and NAFLD [6,7].

Aberrant hepatic p38 activation has long been noticed in mouse models of NAFLD, while circulating FGF21 levels are known to be associated with NAFLD, being involved in the pathogenesis of NAFLD. However, their contribution during the development of fatty liver and the underlying mechanisms remain poorly understood. A very recent study by Hao Ying and colleagues published in *Diabetes* provides new insight into the roles of hepatic p38 and FGF21 in the pathogenesis of NAFLD [8].

p38 is a stress-activated protein kinase responding to different stress stimuli and presents a pivotal role in the regulation of diverse cellular processes. A link between hepatic p38 activation and metabolism has long been reported [9–11]. Nevertheless, the physiologic and pathophysiologic role of p38-mediated stress signalling is not fully understood. Particularly, whether hepatic p38 activation is a cause or consequence of steatosis and insulin resistance remains unknown. In this study, Ying and colleagues demonstrate that hepatic p38 activation by adenovirus-mediated overexpression of MKK6, a major upstream MAP2K of p38, in the liver can result in severe liver steatosis. As loss of hepatic p38α can totally diminish the metabolic effect of adenoviral MKK6, the authors propose that hepatic p38α is the major mediator for the development of liver steatosis. Therefore, they have hypothesized that sustained hepatic p38 activation is a causal driver of liver steatosis and hepatic insulin resistance.

Re-esterification of circulating fatty acids (FAs) due to the dysfunction of the adipose tissue is responsible for about 60% of hepatic triglyceride accumulation in NAFLD. Although it is known that the secretion of hepatokines is dysregulated in NAFLD, how hepatokines are involved in NAFLD development remains elusive [12]. Since obese mice with systemic insulin resistance are usually used for the study of NAFLD, these studies offer only limited insight into the pathogenesis of NAFLD,

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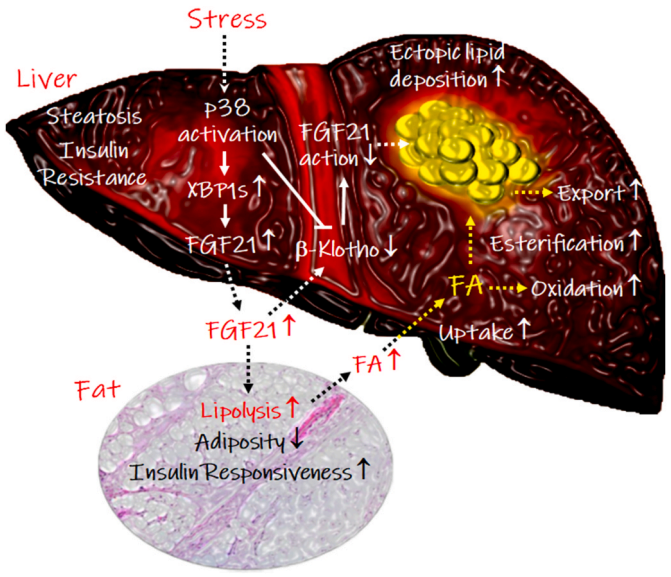

Fig. 1. The pathophysiologic roles of stress kinase p38 and stress hormone FGF21 in the development of hepatic steatosis. Sustained hepatic p38 activation forces the liver to store excess lipid by two mechanisms. It promotes fat mobilization from the adipose tissues to the liver by increasing hepatic expression and secretion of stress hormone FGF21, and impairs the local action of stress hormone FGF21 by increasing the degradation of β-Klotho in the liver. Abbreviations: FA, fatty acid; FGF21, fibroblast growth factor 21; X-box binding protein 1, XBP1.

especially non-obese NAFLD. In this study, Ying and colleagues demonstrate that hepatic p38 activation increases lipolysis in the adipose tissues via liver-derived stress hormone FGF21 rather than inducing adipose insulin resistance, thereby redistributing fat from adipose tissues to liver, suggesting that ectopic hepatic lipid accumulation can be real hepatogenic. The authors also propose that the increased hepatic FGF21 secretion induced by p38 activation may provide a plausible explanation for the lean phenotype observed in non-obese NAFLD.

The phenomenon of "FGF21 resistance" suggested in metabolic disorders, including obesity and NAFLD, is actually not fully understood [13]. In this study, Ying and colleagues show that hepatic p38 activation induces a hepatic "FGF21 resistant" phenotype in mice. They also demonstrate that hepatic p38 activation can facilitate the ubiquitination and degradation of FGF21 receptor cofactor β-Klotho, resulting in decreased β-Klotho protein levels and impaired FGF21 action in the liver. As downregulation of β-Klotho can attenuate hepatic FGF21 action and promote hepatic lipid accumulation, these authors then hypothesize that a defect in hepatic FGF21 action may also contribute to the formation of liver steatosis after hepatic p38 activation [8].

Ying and colleagues have uncovered previously undescribed roles of hepatic stress kinase p38 in regulating whole-body metabolic homeostasis via stress hormone FGF21. In agreement with the notion that disease is often the result of an aberrant or inadequate response to physiologic and pathophysiologic stress, sustained hepatic p38 activation forces the liver to store excess lipid through two mechanisms explained in Fig. 1. Based on the observation that mice with hepatic p38 activation exhibit not only hepatic steatosis but also reduced adiposity, which is similar to those observed in lean NAFLD, these findings may also provide a plausible explanation for the lean phenotype seen in NAFLD. In conclusion, the study by Ying and colleagues not only provides new insight into the molecular basis for liver-fat communication axis that regulates systemic metabolic homeostasis, but also sheds new light on the onset and pathogenesis of NAFLD [8].

Conflict of interest

None.

Funding information

None.

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