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Commentary

Thrombospondin1 as a potential therapeutic target for human nonalcoholic fatty liver disease

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In parallel with the ongoing epidemics of obesity, diabetes and metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), characterized by excess hepatic lipid accumulation in the absence of other causes such as alcohol consumption, is rapidly becoming the most common etiology of chronic liver disease. It is estimatted that NAFLD affects 25% of the general population worldwide and 85–98% of morbidly obese patients[1]. Non-alcoholic steatohepatitis (NASH), a histological subtype of NAFLD, has a potentially progressive course leading to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation, which affects around 1.5–6.5% of the general population[2]. The underlying mechanisms, diagnosis and thrapeutic targets of NAFLD/NASH have attracted extensive attentions. However, despite decades of research, effective therapy for NAFLD/NASH is still lacking.

In this reserach article of *EBioMedicine*, Bai et al. reported that Thrombospondin1 (Thbs1) may serve as a novel biomarker for NAFLD in humans and could be a potential novel therapeutic target for the treatment of this disease[3]. Thbs1 is an extracellular matrix protein released from various types of cells, such as platelets, macrophages, and adipocytes, and participates in a wide range of physiological and pathological processes, including cellular adhesion, angiogenesis, cell migration, tumor growth and metastasis[4]. It was also reported that Thsb1 can be used as a biomarker of obesity and metabolic syndrome [5]. In the current study, authors discovered a novel role of Thbs1 in the pathogenesis of NAFLD. They demonstrated that Thbs1 could serve as a biomarker for hepatic steatosis in humans, and pharmacological and genetic activation of Thbs1 inhibited lipogenesis and attenuated hepatic steatosis. The findings suggested the potential clinical applications of Thbs1 and its peptide mimetics for treating NAFLD and related metabolic diseases.

NAFLD/NASH provides a unique challenge for biomarker and therapy development. To date, liver biopsy remains the gold standard for NAFLD/NASH diagnosis. However, liver biopsy is invasive, may cause bleeding and suffer from sampling bias, and therefore non-invasive diagnostic method is needed[6]. Several steatosis scores based on serum biomarkers have been reported, such as SteatoTest, fatty liver index (FLI), hepatic steatosis index (HSI), and the NAFLD liver fat score (NAFLD-LFS)[7]. However, these scores have not gained much popularity as they do not add much to the information provided by clinical, laboratory and imaging studies done routinely in patients with suspected NAFLD[8]. In this article, Bai et al. found that serum Thbs1 levels are increased in the patients with NAFLD and positively associated with liver steatosis grades measured by liver biopsy diagnosis. Furthermore, serum Thbs1 level in NAFLD patients is decreased following the improvement of liver steatosis after lifestyle intervention. All these data suggeted that Thbs1 may serve as a non-invasive biomarker for diagnosis and quantification of hepatic fat content in NAFLD patients. However, the clinical significance of Thsb1 as a biomarker for hepatic steatosis needs to be further validated.

Bai et al. also demonstrated that pharmacological administration of recombinant human Thbs1 attenuated hepatic steatosis in diet-induced obese mice. Mechanistically, authors showed that Thbs1 inhibited cleavage and processing of SREBP-1 through CD36, leading to a reduction of lipogenesis and hepatic steatosis. More interestingly, treatment with a small peptide mimeitic of Thbs1, ABT-526, had comparable effect on reducing hepatic lipid accumulation compared to Thbs1 overexpression. The safety and activity of ABT-526 have been validated in dogs with naturally occurring malignant cancers [9]. The beneficial effects of Thbs1 on lipid accumulation made it an attractive target for novel drug discovery efforts.

Despite the high prevalence of NAFLD, it doesn't progress for majority of patients and only those with NASH and advanced hepatic fibrosis are at high risk of developing complications of chronic liver disease; hepatic fibrosis is a major predictor of liver-related morbidity and mortality[10]. The real key challenge in the management of NAFLD patients is to differentiate NASH from isolated steatosis. Even more, there are no USA Food and Drug Administration (FDA)-

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approved or European Medicines Agency (EMA)-approved therapies for NASH so far. It is interesting to note in this study that serum levels of Thbs1 are also elevated in advanced NASH subjects compared with normal control and future studies are needed to test the effects of pharmacological Thbs1 on NASH phenotypes.

Declaration of Competing Interest

Authors have nothing to declare.

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