Identifying Soluble Mediators of Nuclear Receptor and Insulin Signaling May Enhance Noninvasive Diagnosis of Fibrosis in Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) represents a liver disease with a rising prevalence worldwide, which is characterized by hepatic steatosis and which carries the risk to progress to nonalcoholic steatohepatitis (NASH) with or without fibrosis, thus promoting the development of hepatocellular carcinoma [1]. The metabolic syndrome implies insulin resistance (IR) and hepatic fatty acid disorders promoting progression to NASH. As the pathogenesis of fibrogenesis in NAFLD and the progression to NASH cirrhosis remain poorly understood, nuclear receptor signaling is now in the focus of NAFLD research [2]. IR as well as fatty acid metabolism are regulated in part by the actions of peroxisome proliferator-activated receptors (PPARs) by inducing enzymes involved in fatty acid oxidation as well as gluconeogenesis [3, 4]. Fibrates act as ligands of PPAR α , but their clinical benefits in the treatment of NAFLD have been rather disappointing [5], whereas a combined PPAR α / δ agonist prevents diet-induced hepatic steatosis and inflammation in rodents [6]. Activation of PPAR α might even prevent or attenuate hepatic fibrosis in NAFLD [7]. PPAR γ expression is increased in steatotic liver tissue, and upon activation with glitazones, PPAR γ improves IR and hepatic steatosis [3]. However, no effects on the clinical course of NASH, especially the progression of fibrosis, could be observed [8]. Nevertheless, data suggest a positive effect of PPAR γ on NASH-related hepatocellular carcinoma [1].

Peptidyl-prolyl *cis-trans* isomerase NIMA-interacting 1 (Pin1) is associated with IR, as Pin1 expression is in-

duced in the nonfasted state and represses the transcriptional expression of PEPCK via the cAMP response element [9]. PEPCK expression is also regulated by PPAR α [4]. In Pin1 knockout mice, PPAR α expression and the expression of its downstream targets were reduced, which was associated with increased steatosis, inflammation and fibrosis in MCD-fed mice [9]. Furthermore, Pin1 binds to insulin receptor substrate 1 (IRS1) and thus enhances insulin sensitivity [10]. Pin1 was also found to inhibit PPAR γ -dependent gene expression in some studies [11]. PPAR agonist treatment induces serum concentration of adiponectin, a soluble adipocytokine with anti-apoptotic properties [12]. In line with this observation, serum adiponectin is inversely correlated with the severity of NAFLD [13, 14]. Therefore, adiponectin might be utilized as a noninvasive marker for NAFLD severity [15].

In this issue of *Digestion*, Cengiz et al. [16] observed a significantly higher expression of Pin1 in the serum of NASH patients compared to controls. In a multivariate analysis, Pin1 was an independent predictor of advanced fibrosis in NAFLD.

Given the growing prevalence of NAFLD, yet the low rate of patients that develop NASH, biomarkers of advanced stages and fibrosis are needed [17]. In addition, Pin1 seems to be a crucial factor within the pathogenesis of many different cancers, and this enzyme may apparently play a role within the progression of liver fibrosis being involved in hepatic stellate cell activation and TGF β 1-mediated signaling [18, 19]. The assessment of serum levels

of caspase-cleaved cytokeratin 18 fragments correlates with histological features of NASH [20, 21]. Other approaches include micro-RNA signatures, proteomics, a combination of fibrosis markers or transient elastography to predict the development of fibrosis in NASH [22–25].

However, limited data are available on biomarkers for fibrosis in this cohort. An approach, in which serum expressed molecules associated with PPAR signaling, like adiponectin or Pin1, might enhance noninvasive diagnostics in NAFLD.

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