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EDITORIAL

Autotaxin, PPARs, and FGF21: An Eye Opener for Progressive Liver Disease?

Autotaxin (ecto-nucleotide pyrophosphatase/phosphodiesterase 2) and its product lysophosphatidic acid[1] have attracted increasing attention on the field of hepatology during the past years after other medical research areas such as cardiology and endocrinology. Still, numerous physiological and pathophysiological roles of autotaxin and lysophosphatidic acid in liver pathology including inflammation, proliferation, fibrosis, cirrhosis, and carcinogenesis are far from being explored. Autotaxin is formed in various organs, particularly in adipose tissue, which under healthy conditions dominates autotaxin serum levels and activity.[1] Notably, up-regulation of hepatic autotaxin expression and secretion into blood (but not bile) has been observed under various pathologic conditions of the liver including nonalcoholic fatty liver disease[2] and chronic cholestatic diseases such as primary biliary cholangitis or primary sclerosing cholangitis,[3,4] and has been shown to be associated with disease severity[2,4] and correlated inversely with prognosis.[3,4]

Autotaxin in plasma forms lysophosphatidic acid in its active site by splitting choline from lysophosphatidylcholine,[1] a phospholipid that is available at abundant (approximately 500 μmol/L) plasma levels and is derived from the major human phospholipid, phosphatidylcholine. Formed lysophosphatidic acid subsequently can bind in a hydrophobic tunnel near the active site and this allows prolonged association of this short-lived agonist with the protein. Although the association of lysophosphatidic acid with autotaxin stimulates the activity, association of bile acids and bile acid–like molecules with the hydrophobic tunnel of autotaxin inhibits its activity.[5] By binding of autotaxin to integrins on the plasma membrane of cells, the enzyme releases lysophosphatidic acid in close proximity to G-protein–coupled lysophosphatidic acid receptors (types 1–6).[1] Intracellular extracellular signal-regulated kinase phosphorylation/activation is a common early event after binding of lysophosphatidic acid to its receptor.[1]

In the present issue of *Cellular and Molecular Gastroenterology and Hepatology*, Qiu et al[6] provide an excellent article summarizing clinical and experimental studies on the role of hepatocyte-secreted autotaxin for progression of nonalcoholic fatty liver disease through autocrine inhibition of the peroxisomal proliferator-associated receptor α (PPARα)/fibroblast growth factor 21 pathway. In short, in 125 obese people, liver biopsy specimens confirmed the formerly described correlation of histologic nonalcoholic fatty liver disease severity with hepatocyte-derived serum autotaxin levels. In 2 established mouse models of nonalcoholic fatty liver disease, Qiu et al showed the critical involvement of hepatocyte-derived autotaxin for nonalcoholic fatty liver disease progression by suppression of hepatic autotaxin expression using viral delivery and use of neutralizing autotaxin antibodies. In particular, defective fatty acid oxidation was improved by these measures. Intriguingly, Qiu et al then showed in the human hepatocellular carcinoma cell line HuH7 a direct link of autotaxin–lysophosphatidic acid to Erk-mediated inhibition of PPARα activity by post-translational Ser phosphorylation and subsequent impairment of PPARα-dependent formation and secretion of potentially protective fibroblast growth factor 21 and its downstream effector adiponectin, being reinstalled by use of neutralizing autotaxin antibodies or knockdown of hepatic autotaxin in nonalcoholic fatty liver disease mouse models.

The present data are highly stimulating and Aimin Xu's team from Hong Kong have to be congratulated for their excellent work.[6] Certainly, a moment of caution has to be included for the generalizability of the described findings because they have been obtained in different models, starting with findings in severely obese people, continuing with mouse models of nonalcoholic fatty liver disease (always controversially discussed), and finishing with an established human liver carcinoma cell line. Still, this article can be praised as a masterpiece of translational research. It remains open whether these findings can be translated to other autotaxin–lysophosphatidic acid–related topics in liver research.[7]

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Conflicts of interest
The authors disclose no conflicts.


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