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Commentary

Lysosomal Acid Lipase Activity: A Tool for the Detection and Management of Fatty Liver Disease?

Charina M. Ramirez[a], Adam M. Lopez[b], Stephen D. Turley[b,*]

[a] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA
[b] Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

The plethora of new publications on non-alcoholic fatty liver disease (NAFLD) in both pediatric and adult populations worldwide is testimony to the scale of this problem (Abd El-Kader and El-Den Ashmawy, 2015; Sanyal et al., 2015). Projections on the numbers of cases as well as related liver transplantations in the coming decades underscore the urgent need for expanded research into the mechanisms through which NAFLD develops and the design of more effective strategies for its management. In this issue of *EBioMedicine*, Baratta et al. present data suggesting that a blood test for lysosomal acid lipase (LAL) activity might serve as a useful tool for these endeavors (Baratta et al., 2015).

Baratta and colleagues screened LAL activity in substantial numbers of NAFLD (n = 240) and NASH (n = 35) patients, as well as healthy subjects (n = 100), using a modified, validated technique that employs dried blood spots (Hamilton et al., 2012). The data show that NAFLD patients had significantly lower LAL activities than healthy subjects, and that activities were even lower in NASH patients. This study's findings have important implications for the potential use of blood LAL activity as a screen in the detection and management of NAFLD. Inherent in this premise is the assumption that the activity of LAL detected in dried blood spots faithfully reflects that in cells throughout the body, particularly in the liver.

LAL plays a key role in the regulation of intracellular lipid homeostasis. Specifically, it hydrolyzes esterified cholesterol (EC) and triglycerides (TG) contained within lipoproteins, particularly low density lipoproteins (LDL) and related particles, that are taken up by cells via receptor-mediated and bulk-phase endocytosis. Mutations in LIPA, the gene that encodes LAL, result in either Wolman Disease, or in Cholesteryl Ester Storage Disease (CESD). Whereas WD is a severe, early onset illness caused by complete loss of LAL activity, CESD is a milder, later-onset disease resulting from partial LAL deficiency that is often accompanied by dyslipidemia and a predisposition to atherosclerosis (Scott et al., 2013; Grabowski et al., 2015). Hepatomegaly and a massive increase in tissue EC content and also in TG levels, especially in the liver, are hallmark features of both disorders which can be treated with enzyme replacement therapy (Balwani et al., 2013). One of the more notable findings in the present study was that in the 50% of the NAFLD patients with LAL activities below the median, serum LDL-cholesterol levels were higher. However, the proportion of subjects in this group receiving statin therapy (28.0%) was significantly lower than in the other half of patients whose LAL activities were above the median (43.3%). The implied benefit of statin therapy in NAFLD patients here raises the question of whether this is also the case in individuals with CESD. As recently discussed (Reiner et al., 2014), statin therapy may be detrimental in individuals with CESD. To the extent that statins increase receptor-mediated clearance of LDL, particularly in the liver, an accelerated rate of lysosomal EC entrapment could likely increase liver damage in the face of a reduction in the circulating LDL-cholesterol level.

Perhaps the most fundamental question raised by the data from the current study centers on the mechanism(s) that causes LAL activity to fall in NAFLD and NASH patients, and which might explain their apparent favorable response to statins. Answering this requires delineation of how intrahepatic cholesterol metabolism changes at a biochemical and molecular level in NAFLD and NASH. Several published studies provide a fascinating insight into the nature of these changes. Detailed data for mRNA and protein levels for a constellation of genes involved in regulating sterol homeostasis in the liver revealed, amongst other changes, an elevated rate of cholesterol synthesis, depressed LDL-receptor expression, and reduced levels of activity of several key sterol transporters in NAFLD/NASH patients (Min et al., 2012). These changes parallel those known to occur in CESD. However, there is one particular difference between CESD and NAFLD/NASH patients that warrants emphasis. In CESD, hepatic EC levels are often elevated more than 100-fold, with accompanying dramatic increases in tissue TG levels along with, at most, a marginal rise in the concentration of unesterified cholesterol (UC). Lipidomic analyses of liver tissue from NAFLD and NASH patients revealed that the dramatic rise in TG levels was accompanied by an elevated UC concentration, particularly in the subjects with NASH (Puri et al., 2007). Surprisingly, hepatic EC levels in these patients were not different from those in control subjects. The potential consequences of the rise in hepatic UC levels depend partly on the subcellular site where this buildup occurs. If increased UC concentrations lead to down regulation of hepatic LDLR expression, then conceivably lower rates of LDL-EC and LDL-TG entry into the lysosomal compartment might lead to an adaptive fall in LAL activity.

While further exploration of these mechanisms is essential, so too is the development of reliable biomarkers for identifying NAFLD/NASH patients and monitoring their response to treatment. The results of the current investigation demonstrate the potential of blood LAL activity in meeting this need.

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* Corresponding author.

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Declaration of Interests

None.

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