

Hepatic Lysosomal Acid Lipase and lipophagy in the progression of NAFLD

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Lysosomal Acid Lipase (LAL) is an acidic enzyme that degrades cholesterol-ester and triglyceride inside lysosomes. Both genetic LAL deficiency and non-alcoholic fatty liver disease (NAFLD) are featured by lipid accumulation in hepatocyte leading to steatosis and eventually liver failure. Recently, a deficit in blood LAL activity was found in NAFLD patient (1). Lipophagy plays a pivotal role in degradation of lipids in the liver and consists in autophagic sequestration of lipid droplets and their degradation inside lysosomes by LAL (2). p62 serves as an autophagy/lipophagy receptor for selective autophagy and accumulates when the autophagy is blocked. We aimed to evaluate the hepatic expression of LAL in NAFLD patients and healthy subjects and to verify its association with histopathological features. Furthermore, we aimed to compare LAL levels with autophagic flux and lysosomal compartment status (LAMP1-positive vesicles). LAL expression was reduced in NAFLD patients with respect to healthy subjects ($p < 0.001$), in patients with microvesicular steatosis $\geq 25\%$ with respect to those with $< 25\%$ ($p < 0.01$), and inversely correlated with NAFLD activity ($r = -0.52$; $p < 0.001$). p62 expression increased with the progression of NAFLD ($r = 0.47$; $p < 0.001$) and LAMP1-positive fatty vacuoles was inversely correlated with LAL expression ($r = -0.35$; $p = 0.01$). Hyperdense vacuoles resembling typical lipolysosome and autophagosomes were observed with TEM analysis and accumulates in NAFLD patients. These results show that LAL expression is reduced in NAFLD patients and associated with features of genetic LAL deficiency and NAFLD activity. A lipophagy impairment, probably due to LAL dysfunction, could exert a pathogenic role in NAFLD development.

References

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Keywords

Non-alcoholic fatty liver disease, lysosomal acid lipase, lipophagy