Hepatic stellate cells retain the capacity to synthesize retinyl esters and to store neutral lipids in small lipid droplets in the absence of LRAT

ABSTRACT

Hepatic stellate cells (HSCs) play an important role in liver physiology and under healthy conditions they have a quiescent and lipid-storing phenotype. Upon liver injury, HSCs are activated and rapidly lose their retinyl ester-containing lipid droplets. To investigate the role of lecithin:retinol acyltransferase (LRAT) and acyl-CoA:diacylglycerol acyltransferase 1 (DGAT1) in retinyl ester synthesis and lipid droplet dynamics, we modified LC–MS/MS procedures by including multiple reaction monitoring allowing unambiguous identification and quantification of all major retinyl ester species. Quiescent primary HSCs contain predominantly retinyl palmitate. Exogenous fatty acids are a major determinant in the retinyl ester species synthesized by activated HSCs and LX-2 cells, indicating that HSCs shift their retinyl ester synthesizing capacity from LRAT to DGAT1 during activation. Quiescent LRAT−/− HSCs retain the capacity to synthesize retinyl esters and to store neutral lipids in lipid droplets ex vivo. The median lipid droplet size in LRAT−/− HSCs (1080 nm) is significantly smaller than in wild type HSCs (1618 nm). This is a consequence of an altered lipid droplet size distribution with 50.5 ± 9.0% small (≤ 700 nm) lipid droplets in LRAT−/− HSCs and 25.6 ± 1.4% large (1400–2100 nm) lipid droplets in wild type HSC cells. Upon prolonged (24 h) incubation, the amounts of small (≤ 700 nm) lipid droplets strongly increased both in wild type and in LRAT−/− HSCs, indicating a dynamic behavior in both cell types. The absence of retinyl esters and reduced number of lipid droplets in LRAT-deficient HSCs in vivo will be discussed.

Keyword: Hepatic stellate cells; LRAT; DGAT1; Retinyl esters; Lipid droplets; Lipidomics