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Hyodeoxycholic acid ameliorates nonalcoholic fatty liver disease by inhibiting RAN-mediated PPARα nucleus-cytoplasm shuttling

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Nonalcoholic fatty liver disease (NAFLD) is usually characterized with disrupted bile acid (BA) homeostasis. However, the exact role of certain BA in NAFLD is poorly understood. Here we show levels of serum hyodeoxycholic acid (HDCA) decrease in both NAFLD patients and mice, as well as in liver and intestinal contents of NAFLD mice compared to their healthy counterparts. Serum HDCA is also inversely correlated with NAFLD severity. Dietary HDCA supplementation ameliorates diet-induced NAFLD in male wild type mice by activating fatty acid oxidation in hepatic peroxisome proliferator-activated receptor α (PPARα)-dependent way because the anti-NAFLD effect of HDCA is abolished in hepatocyte-specific *Pparα* knockout mice. Mechanistically, HDCA facilitates nuclear localization of PPARα by directly interacting with RAN protein. This interaction disrupts the formation of RAN/CRM1/PPARα nucleus-cytoplasm shuttling heterotrimer. Our results demonstrate the therapeutic potential of HDCA for NAFLD and provide new insights of BAs on regulating fatty acid metabolism.

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in clinic with a spectrum of disorders ranging from simple fatty liver, nonalcoholic steatohepatitis, and fibrosis/cirrhosis. Currently, NAFLD affects nearly a quarter of the global population, and its prevalence is surging[1–3]. Emerging evidence has indicated the dynamic alterations in bile acid (BA) profiles throughout NAFLD progression[4,5]. Besides as digestive detergents, BAs are important signaling molecules to regulate lipid metabolism, glucose homeostasis, and immune response through acting on their receptors such as G protein-coupled bile acid receptor 1 (GBPAR1 or TGR5) and farnesoid X receptor

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