Hepatic management of toxic sterols after acute deletion of Cyp51 from cholesterol synthesis

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Abstract

Lanosterol 14α-demethylase (CYP51), a key enzyme in cholesterol synthesis, is essential for normal liver function. Reduced CYP51 activity leads to metabolism-associated liver disease and ultimately hepatocellular carcinoma, yet the hepatocellular processes most affected and their crosstalk with other liver cell types remain poorly defined. Here, we present a new inducible liver-specific Cyp51 KO mouse (iLKO) model designed to study how acute disruption of cholesterol synthesis is managed in the adult liver. Doxycycline-inducible deletion minimizes developmental confounders of albumin-Cre models and enables isolation of viable primary hepatocytes. iLKO hepatocytes and liver tissue showed efficient CYP51 depletion with marked accumulation of lanosterol and 24,25-dihydrolanosterol, whereas hepatic cholesterol levels remained unchanged or only mildly reduced, indicating compensatory uptake and/or pathway rerouting. Histology and transmission electron microscopy revealed hepatomegaly with mild portal inflammation, ductular reaction, endoplasmic reticulum dilation, mitochondrial swelling, and increased nuclear lipid droplets, consistent with adaptation to endoplasmic reticulum stress but without overt fibrosis at the studied time points. Notably, crystal-like inclusions—particularly in Kupffer cells—were observed. Although MALDI-TOF mass spectrometry imaging could not determine their exact composition, their presence in the context of toxic sterol overload strongly suggests noncholesterol sterol crystallization as a previously unrecognized trigger of inflammation. In summary, the iLKO model allows dissection of sterol toxicity independently of developmental effects and provides mechanistic insight into how disrupted cholesterol synthesis in adult hepatocytes initiates sterol-driven cellular stress and inflammation that predispose to metabolism-associated liver disease and hepatocellular carcinoma.