NASH

KLF6 activates PPAR α signalling in hepatic steatosis

Krüppel-like factor 6 (KLF6) induces metabolic abnormalities in NAFLD via post-transcriptional activation of peroxisome proliferator-activated receptor α (PPAR α) signalling. These new findings show that KLF6 is a novel regulator of hepatic glucose and lipid metabolism in NAFLD.

NAFLD can progress to NASH, although the mechanism is poorly understood. “Mounting evidence linked KLF6 to regulation of glucose and lipid metabolism, and this study was intended to further clarify mechanisms accounting

for that regulation,” explains author Scott Friedman.

The researchers used genetically altered mice with defects in Klf6 expression—one mouse model with global depletion of Klf6 in all cells, the other with Klf6 deficiency in hepatocytes only—to understand the link between Klf6 and glucose and lipid regulation. The expression of KLF6 target genes was also quantified in liver samples from 28 patients with NAFLD.

Klf6 depletion in mice led to reduced body fat content and improved tolerance to glucose and insulin. Moreover, these

mice were protected from hepatic steatosis induced by a high-fat diet.

In hepatocytes, Klf6 deficiency led to reduced expression of PPAR α -regulated genes (*Trb3*, *Pepck*) and diminished levels of PPAR α protein. Interestingly, PPAR α mRNA levels were unaffected; this observation could be partly explained by the finding that Klf6 repressed miRNA-10b (characterized as a repressor of PPAR α), which in turn led to the induction of PPAR α .

Parallel links between KLF6 and PPAR α signalling were also observed in human fatty livers. In patients with NAFLD, KLF6 mRNA expression was associated with expression of *TRB3* mRNA and correlated with *PEPCK* expression. Furthermore, in human NAFLD with histologically confirmed hepatic inflammation, expression of KLF6, PPAR α protein, and *TRB3* and *PEPCK* mRNA was increased, with decreased miRNA-10b expression, which together indicate that KLF6 affects hepatic insulin response and gluconeogenesis.

Further work will help to “disentangle the multiple convergent pathways that conspire to generate NASH and its complications” notes Friedman.

Katrina Ray

KLF6 and PPAR α immunohistochemistry reveals increased protein expression and inflammation in human liver tissue from patients with NAFLD. Increased expression of cytoplasmic and nuclear KLF6 and PPAR α proteins is observed in individuals with inflammation (Brunt criteria, inflammation ≥ 1 ; magnification $\times 20$). Image courtesy of S. Friedman.

Original article Bechmann, L. *et al.* Post-transcriptional activation of PPAR α by KLF6 in hepatic steatosis. *J. Hepatol.* doi:10.1016/j.jhep.2013.01.020