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LIVER

Sussing out statins in cirrhosis—KLF2 is the key

Upregulation of the transcription factor Krüppel-like factor 2 (KLF2) has been shown to improve liver fibrosis and have vasoprotective effects in experimental models of cirrhosis, according to new research published in *Gut*. Moreover, the new findings highlight that simvastatin, a known inducer of KLF2, could be used as treatment for cirrhosis and portal hypertension in the future.

"Cirrhosis and its main complication, portal hypertension, are nowadays considered a serious clinical problem with high morbidity and mortality," explains corresponding author Jordi Gracia-Sancho. KLF2 has previously been identified as a key component of the hepatic endothelium where its expression is thought to combat the damage that occurs as cirrhosis progresses. Furthermore, statins have been shown to reduce portal pressure as well as have protective effects on the endothelium (via KLF2). As such, the researchers wanted to determine the molecular mechanisms of increased induction of KLF2 in the liver.

The investigators explored the role of KLF2 in both *in vitro* and *in vivo* models of liver cirrhosis, increasing expression of KLF2 either by pharmacological methods (via simvastatin) or use of adenoviral vectors. For cell culture, they used a variety of techniques including coculture in transwells and in a 3D cell culture chamber with microfluidics (mimicking the liver sinusoid environment) to determine how different cells interacted.

Upregulation of KLF2 led to marked improvements in portal hypertension and fibrosis in rats with cirrhosis. The investigators found that KLF2 overexpression led to a 41% reduction in liver fibrosis and a 15% decrease in portal pressure (owing to effects on portal blood flow, hepatic vascular resistance and endothelial function).

Experiments *in vitro* revealed that these beneficial effects of KLF2 overexpression were probably because of hepatic stellate cell (HSC) inactivation and apoptosis alongside a reduction in hepatic oxidative stress. Moreover, according to coculture studies, this change in HSC phenotype was also found to paracrinally improve the function of liver sinusoidal endothelial cells, rectifying their dysfunctional phenotype observed in cirrhosis.

"Our study proposes the use of simvastatin, or other KLF2 activators, as a promising therapy not only to improve portal hypertension, but also to potentiate cirrhosis regression," says Gracia-Sancho. Further work is needed to confirm these findings in a clinical setting and show whether statins can move from bench to bedside in the management of cirrhosis.

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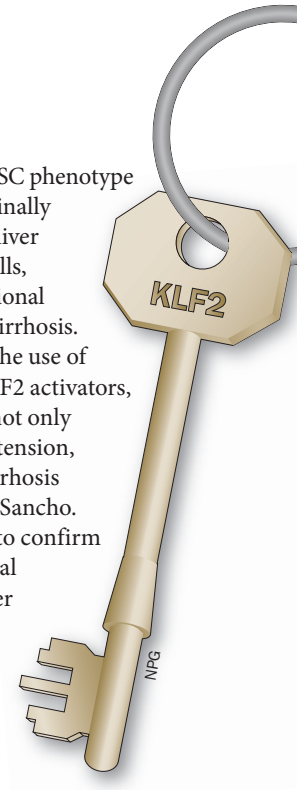

Original article Marrone, G. *et al.* KLF2 exerts antifibrotic and vasoprotective effects in cirrhotic rat livers: behind the molecular mechanisms of statins. *Gut* doi:10.1136/gutjnl-2014-308338