

## LIVER

**GROWTH HORMONE  
IN LIVER FIBROSIS**

Resistance to growth hormone increases liver fibrosis in a mouse model of inflammatory cholestasis, reports a study recently published in *Hepatology*.

Growth hormone resistance is known to be associated with liver fibrosis; however, whether the resistance is simply the result of hepatocyte malfunction owing to cirrhosis or if it has a causal role in disease development has been debated. To determine the nature of this relationship, Emilio Casanova and colleagues crossed mice lacking the gene that encodes the growth hormone receptor (*Ghr*<sup>-/-</sup>) with a mouse model of inflammatory cholestasis and liver fibrosis (*Mdr2*<sup>-/-</sup>).

The resulting double knockout mice had raised serum levels of markers associated with liver damage and cholestasis, extensive bile duct proliferation and increased collagen deposition in the liver compared with *Mdr2*<sup>-/-</sup> mice. This finding suggests that growth hormone resistance increases the severity of the liver fibrosis phenotype. Furthermore, *Ghr*<sup>-/-</sup> mice that were fed a diet containing 1% cholic acid had increased levels of liver damage, biliary infarcts and reactive oxygen species, as well as increased hepatocyte apoptosis. In an *in vitro* experiment, hepatocytes isolated from *Ghr*<sup>-/-</sup> mice that were treated with deoxycholic acid, transforming growth factor  $\beta$  or TNF (either alone or in combination) had reduced cell viability compared with wild-type hepatocytes. Together, these results indicate that loss of *Ghr* leaves mice more susceptible to liver injury from bile acids and cytokines compared with wild-type mice.

“Our results suggest that growth hormone resistance has a causal role in the development of liver fibrosis rather than being a mere consequence of the disease,” says Casanova. “Abrogation of growth hormone signalling renders the hepatocytes more susceptible to insults, such as bile acids, therefore contributing to the progression of liver fibrosis.”

Next, the team would like to improve understanding of the link between liver fibrosis and growth hormone resistance at the cellular level. To achieve this aim, they plan to investigate the genetics of growth hormone signalling in the different types of liver cells.

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**Original article** Stiedl, P. *et al.* Growth hormone resistance exacerbates cholestasis-induced murine liver fibrosis. *Hepatology* doi:10.1002/hep.27408