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LIVER

Activation of NF-κB signaling in hepatocytes induces liver fibrosis

Insights into the molecular pathways that underlie the development of liver fibrosis have been revealed in a new study by Thomas Wirth and colleagues published in *Hepatology*. "Hepatic activation of NF-κB signaling is sufficient to induce moderate liver damage, recruitment of inflammatory cells, hepatocyte proliferation and, ultimately, spontaneous liver fibrosis in a mouse model," explains Wirth.

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Liver fibrosis occurs in many chronic liver diseases (including hepatitis B or C and nonalcoholic steatohepatitis) and is a major cause of liver-related mortality. But exactly how hepatocellular injury leads to liver fibrosis is currently unclear.

To study the role of NF-κB in liver fibrosis, Wirth *et al.* generated mice that expressed constitutively active Ikk2—part of the IKK complex that is the master regulator of NF-κB activation—under the control of an inducible promoter, and specifically in hepatocytes.

Using this model, the authors found that, with 'switched on' gene expression, activation of NF-κB specifically in hepatocytes led to the development of liver inflammation, subsequent liver fibrosis and mild chronic hepatitis in the mice. Moreover, microarray analysis revealed upregulation of genes involved in the hepatocyte stress response, inflammation and chemotaxis in these mutant mice, which was reversed once transgene expression was 'switched off'.

Depletion of macrophages (by clodronate liposomes) attenuated NF-κB-induced fibrogenesis, suggesting that these inflammatory cells are involved in the development of liver fibrosis.

As both NF-κB depletion and activation have been shown to lead to liver fibrosis, Wirth warns, "NF-κB function could be a double-edged sword, with unbalanced NF-κB signaling leading to liver injury and probably contributing to the development of end-stage liver disease."

The authors now plan to elucidate the precise role of NF-κB activation in the development of human liver disease. "An ultimate goal will be to develop selective modification of the NF-κB system as a treatment to ameliorate liver fibrosis development in chronic liver diseases," adds Wirth.

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Original article Sunami, Y. *et al.* Hepatic activation of IKK/NF-κB signaling induces liver fibrosis via macrophage-mediated chronic inflammation. *Hepatology* doi:10.1002/hep.25711

Further reading Luedde, T. & Schwabe, R. F. NF-κB in the liver—linking injury, fibrosis and hepatocellular carcinoma. *Nat. Rev. Gastroenterol. Hepatol.* **8**, 108–118 (2011)