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LIVER

Reprogramming a hepatocyte's memory of liver disease

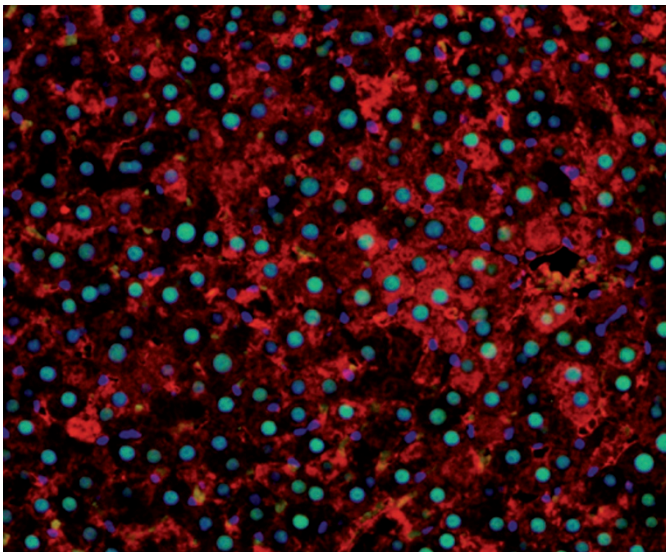

Image courtesy of I. J. Fox & A. Soto-Gutierrez

A new study published in *The Journal of Clinical Investigation* demonstrated the downregulation of a network of hepatocyte-enriched transcription factors in damaged hepatocytes that had been isolated from a rat model of chronic liver injury. Conversely, the forced re-expression of one factor, hepatocyte nuclear factor 4 alpha (Hnf4a), improved cellular function and reversed liver failure.

Carbon tetrachloride (CCl_4) administration in rats reproduces aspects of advanced degenerative liver disease seen in humans, including irreversibly decompensated hepatocytes. Using this model, Nishikawa and colleagues found that in association with end-stage chronic liver disease, a network of transcription factors expressed within hepatocytes were downregulated; these factors included those important to hepatocyte development such as *Hnf4a*, *Foxa2*, *Cebpa*, *Ppara* and *Hnf1a*. The effect could still be observed 4 weeks after CCl_4 discontinuation.

"We wondered whether the damaged cells could be reprogrammed in the same way scientists have been able to reprogramme somatic cells into stem cells or into cells representing other lineages," explains corresponding author Ira Fox (University of Pittsburgh, PA, USA). Re-expression of Hnf4a in cultured hepatocytes from animals with fatally decompensated liver function restored the expression of several other previously downregulated transcription factors and improved cell function.

In the rat model of liver failure, hepatocytes were 'reprogrammed' by injecting animals with adeno-associated viral vectors expressing Hnf4a. This treatment prolonged the survival of injected animals and improved liver function compared with untreated rats, as measured by an increase in clotting factors and liver protein expression. When isolated, hepatocytes from treated animals exhibited normalized cell function and gene expression compared with cells from control animals.

Interestingly, reprogrammed hepatocytes did not demonstrate increased proliferation, although reduced apoptotic cell death was evident. "Our studies showed that the animals didn't get better as a result of stem cell activation or regeneration by growing new liver cells. Instead, the diseased cells had healed," says Fox.

The precise molecular mechanism responsible for the disruption of the hepatic transcription factor network in liver injury remains to be determined. Likewise, it is not clear why dysfunctional hepatocytes cannot seem to restore normal gene function independently.

"We are now looking for the signal pathways that cause hepatocytes to fail and other pathways that allow restored hepatocytes to resolve fibrosis," concludes Fox. The authors hope that these investigations will provide therapeutic candidates for advanced drugs that can specifically target pathways mediating liver fibrosis and hepatocyte damage.

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Original article Nishikawa, T. *et al.* Resetting the transcription factor network reverses terminal chronic hepatic failure. *J. Clin. Invest.* doi:10.1172/JCI73137