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LIVER

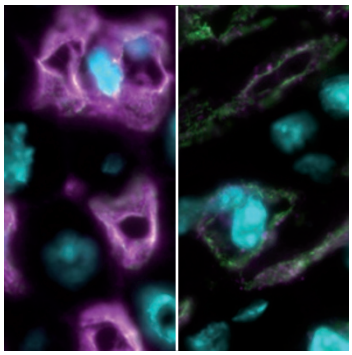
Loss of integrin β1 impairs liver regeneration and HCC progression

Nanoparticles optimised for liver-specific delivery of integrin β1 (*Itgb1*) siRNA reveal that loss of *Itgb1* impairs hepatocyte survival and proliferation after liver injury. In addition, progression of hepatocellular carcinoma (HCC) is retarded after *Itgb1* loss owing to decreased proliferation and increased apoptosis of tumour cells.

Although integrins are known to have an important role in highly proliferative cells, little was known about their function in quiescent or slowly proliferating organs. In the first of two complementary papers published in *Nature Communications*, Speicher *et al.* compared phenotypes of short-term loss of *Itgb1* by using a traditional inducible knockout approach and also via lipid-based nanoparticles for targeting *Itgb1* siRNA to the liver. Mice in both groups were subject to partial hepatectomy and harvested 48 h later. A phenotype of substantial necrosis with strongly impaired hepatocyte proliferation occurred in both groups due to suppressed hyperproliferation and elevated apoptosis. The siRNA approach conferred a milder phenotype with no associated mortality (47% of *Itgb1* knockout mice died 24–48 h after partial hepatectomy).

The advantage of the milder phenotype was that later time points could be studied to elucidate the downstream effects of *Itgb1* knockdown. Loss of integrin β1 was found to inhibit the phosphorylation of two molecules crucial to hepatocyte proliferation, c-Met and epidermal growth factor receptor, blocking their downstream signalling pathways.

In the second paper by Bogorad *et al.*, siRNA knockdown of *Itgb1* confirmed the observation that loss of integrin β1 results in impaired proliferation, which can affect liver homeostasis. Long-term exposure to *Itgb1* siRNA was assessed in normal mice and in a mouse model of HCC.



Itgb1 expression in hepatocytes from an siRNA control (left) and knockdown (right) mouse. Permission obtained from Nature Publishing Group © Bogorad R. L. *et al. Nat. Commun.* doi:10.1038/ncomms4869

Normal mice exposed to *Itgb1* siRNA for more than 7 weeks had distorted liver architecture and elevated serum levels of aminotransferases. In the HCC mouse model, tumour progression was substantially limited in groups that received either 4 or 5 weekly *Itgb1* siRNA injections; alpha-fetoprotein levels (a marker of HCC) and liver weight (which correlates with tumour burden) were substantially reduced compared with the siRNA control group. Subsequent experiments showed that this anti-tumour phenotype was due to lower activation of β-catenin and MET.

These studies reveal that integrin expression is important to liver homeostasis. The loss of integrin β1 impairs normal regenerative processes, but during tumorigenesis (where there is aberrant regeneration) loss of integrin β1 is beneficial as it inhibits HCC progression.

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Original articles Speicher, T. *et al.* Knockdown and knockout of β1-integrin in hepatocytes impairs liver regeneration through inhibition of growth factor signalling. *Nat. Commun.* doi:10.1038/ncomms4862 | Bogorad, R. L. *et al.* Nanoparticle-formulated siRNA targeting integrins inhibits hepatocellular carcinoma progression in mice. *Nat. Commun.* doi:10.1038/ncomms4869