HEPATOCELLULAR CARCINOMA

Cadherin-17: a promising target for therapy of HCC

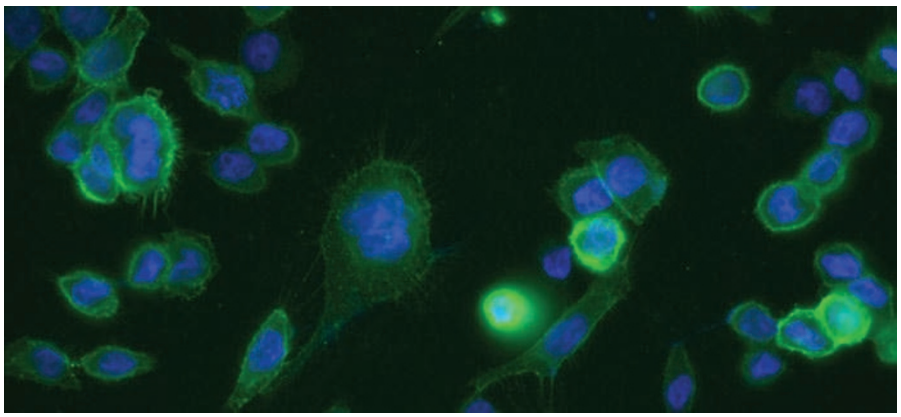
Hepatocellular carcinoma (HCC) is often at an advanced stage before it is diagnosed and at this stage curative therapies are generally ineffective. Ling Xiao Liu and colleagues now report that cadherin-17 (*CDH17*), which encodes a cell surface adhesion molecule not found in healthy adult liver, is a novel oncogene in HCC and is an attractive target for therapy of this aggressive malignancy.

Liu *et al*. found that when CDH17 was overexpressed in immortalized liver progenitor cells and implanted into mice, the cells gave rise to subcutaneous tumors. Analysis of 46 pairs of tumor and adjacent liver tissue samples taken from patients with HCC who had received curative therapy showed that overexpression of CDH17 was associated with advanced tumor stages and with tumor venous invasion, and that over half the patients had genomic amplification of the *CDH17* gene in their tumors.

"To prove the concept that silencing CDH17 expression in HCC can inhibit tumor growth, we used two short-hairpin RNA (shRNA) knockdown approaches (termed shRNA and shRNAmir) to evaluate the therapeutic potential of targeting CDH17," explains John Luk, corresponding author on the paper. Knockdown of CDH17 markedly reduced the tumorigenic and metastatic properties of HCC cell lines that had strong expression of CDH17 and a highly malignant phenotype. This was confirmed *in vivo* when CDH17-expressing HCC cells that had been transduced with *CDH17* shRNA were transplanted into nude mice; tumor growth was minimal compared with that seen in mice that were transplanted with mock-transfected or untreated HCC cells. In addition, no lung metastases were seen in the *CDH17* shRNA treated group. *In vivo* delivery of *CDH17* shRNAmir also impeded the growth of established HCC tumor xenografts. Patients with HCC often have loss of the tumor suppressor p53 in their tumors, and Liu *et al*. also showed that targeting *TP53* with rAAV-TP53 in combination with *CDH17* shRNAmir further reduced tumor size in the xenograft model.

"Since RNAi and gene therapies are still experimental approaches, we have developed monoclonal antibodies that target a putative therapeutic epitope on the CDH17 antigen in human HCC. These antibodies have antitumor effects against metastatic HCC *in vitro* and *in vivo* and we plan to use them to treat patients with HCC and high tumor levels of CDH17 in the near future," comments Luk.

Ezzie Hutchinson



Credit: L. X. Liu

Original article Liu, L. X. *et al*. Targeting cadherin-17 inactivates Wnt signaling and inhibits tumor growth in liver carcinoma. *Hepatology* **50**, 1453–1463 (2009)