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HEPATOCELLULAR CARCINOMA

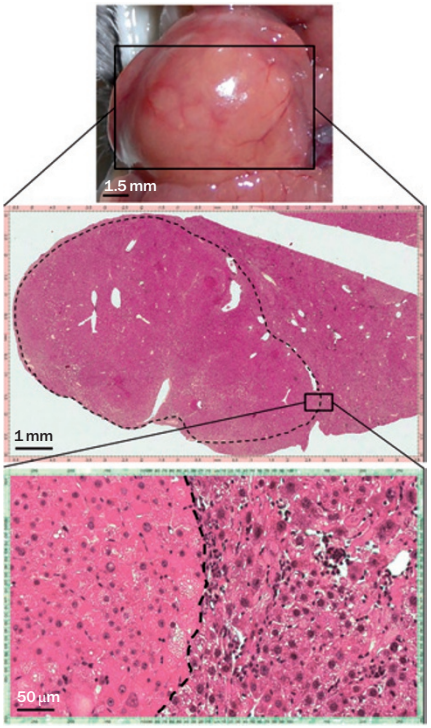
Could antiplatelet drugs be used to prevent HBV-associated hepatocellular carcinoma?

New findings indicate that platelets could have a key role in the pathogenesis of HBV-associated hepatocellular carcinoma (HCC), potentially opening the door for antiplatelet therapy in patients with chronic HBV infection.

"So far, there are no FDA-approved agents able to prevent HCC in the context of chronic liver damage, so the topic of chemoprevention is a clear unmet need," explains Josep Llovet, an expert in HCC working at Hospital Clínic, Barcelona, Spain, and Mount Sinai, New York, USA. In a recent study, treatment with aspirin and clopidogrel prevented progression to HCC in a mouse model of chronic HBV infection.

Sitia *et al.* used a transgenic mouse model of chronic HBV infection that progresses to HCC (lineage 107-5). The study included 540 animals: 110 control mice; 110 mice that received diluents; 110 sham mice; 50 mice that received aspirin; 50 mice that received clopidogrel; and 110 mice that received aspirin and clopidogrel. Treatment was started after the induction of hepatitis and continued indefinitely. Various assays were used to assess the effects of these treatments.

As the mice receiving the combination therapy showed the greatest improvements in the early stages of the study, the researchers focused on this treatment strategy. They found that the mice that received the combination aspirin–clopidogrel therapy (1 mg/kg of each drug daily) had limited persistent liver injury as a result of reduced accumulation of HBV-specific $CD8^+$ T cells and the HBV-nonspecific inflammatory cells they recruit. These mice also had reduced compensatory hepatocyte proliferation and severity of liver fibrosis. The combination therapy prevented the progression to HCC and improved overall survival without causing bleeding. By day 510, 75% of the mice treated with diluents had died and the remaining animals showed signs of cachexia. Only 20% of the mice treated with aspirin–clopidrogrel had died at day 520 and none had cachexia. Of the 15 mice treated with combination therapy that survived to day 600 (at which point they were euthanized), 10 were free of HCC and the other 5 had only a few, small tumours.



HCC in an HBV-transgenic mouse. Top: a large tumour lesion in a representative liver lobe from a 107-5 transgenic mouse (treated with diluents and sacrificed 450 days after disease onset). Middle and bottom: higher magnification micrographs reveal a large (>8.5 mm diameter) well-differentiated HCC surrounded by inflamed liver tissue typical of chronic hepatitis. H&E staining. Courtesy of G. Sitia and L. G. Guidotti.

"The observation that antiplatelet therapy inhibits HCC development unprecedently identifies platelets as key players in the pathogenesis of HBV-associated liver cancer and reinforces the notion that the cellular immune response is sufficient to induce liver cancer during chronic viral hepatitis," says corresponding author Luca Guidotti (San Raffaele Scientific Institute, Milan, Italy, and Scripps Research Institute, La Jolla, USA).

The investigators also used the aspirin–clopidogrel therapy in a mouse model of chemical hepatocarcinogenesis to test whether the effect of the antiplatelets is unrelated to their effect on $CD8^+$ T-cell-induced hepatic immunopathology. Mice from the lineage 107-5 were treated with diluent or aspirin and clopidogrel and were gavaged with carbon tetrachloride twice weekly for 16 weeks. By day 330, the number of HCCs and the extent of fibrosis were comparable between the two groups. "The finding also indicates that preventing HCC development in mice undergoing immune-mediated chronic hepatitis relies on the capacity of antiplatelet therapy to limit the severity of immune-mediated chronic hepatitis," explains Guidotti.

"This study provides the proof-of-principle for exploring the compounds in early clinical trials," says Llovet. "Nonetheless, there are some specific concerns in the area of HCC." Most HCCs develop in patients with cirrhosis, who are very sensitive to NSAIDs such as aspirin, which can lead to renal failure and mortality in these patients. Llovet recommends that if this therapy is considered in humans, it should first be tested in patients with chronic hepatitis B without cirrhosis.

Guidotti and co-workers are now using multiphoton intravital liver microscopy to dissect the molecular basis of the effect of antiplatelet therapy on the HBV-specific $CD8^+$ T cells, which might help in the design of more specific and potentially safer drugs. "The results of our work suggest that drugs targeting platelet function might be a therapeutic option in patients with chronic HBV infection," concludes Guidotti.

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Original article Sitia, G. *et al.* Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1209182109