

# Prevention of chronic HBV infection induced hepatocellular carcinoma development by using antiplatelet drugs

Kuan-Han Lee<sup>1,2</sup>, Chin-Jen Wu<sup>3</sup>, Clay C. C. Wang<sup>4</sup>, Jui-Hsiang Hung<sup>2,5</sup>

<sup>1</sup>Institute of Pharmaceutical Science, Chia Nan University of Pharmacy and Science, Tainan, Taiwan; <sup>2</sup>Drug Discovery and Development Center, Chia Nan University of Pharmacy and Science, Tainan, Taiwan; <sup>3</sup>Department of QC/R&D, Kaiser Pharmaceutical CO., LTD., Tainan, Taiwan; <sup>4</sup>Department of Pharmacology and Pharmaceutical Sciences, University of Southern California, School of Pharmacy, Los Angeles, CA, USA; <sup>5</sup>Department of Biotechnology, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

Corresponding to: Jui-Hsiang Hung. Department of Biotechnology, Chia Nan University of Pharmacy and Science, Tainan, Taiwan, R.O.C. Email: hung86@mail.chna.edu.tw.



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Hepatocellular carcinoma (HCC) is a common malignancy affecting approximately one million people worldwide annually. It is one of the most common causes of cancer morbidity and mortality in Asia and Africa. The successful control of HCC in children after HBV vaccination further supports a role of chronic HBV infection in the development of HCC. Known risk factors for HCC include chronic viral infection, cirrhosis, extensive alcohol intake, non-alcoholic fatty liver disease, certain inherited metabolic conditions, environmental exposure, and transgenic oncogenes (1-4). HBV is considered a major etiological factor in the development of HCC. Patients with chronic HBV infection carry a high risk of developing cirrhosis and HCC. Chronic HBV carriers have a greater than 100 fold increased relative risk of developing HCC, the direct effect of the virus itself, or it may be an indirect effect, through the process of the inflammation, regeneration and fibrosis associated with cirrhosis due to the HBV infection may be involved in HCC development.

Chronic infection with HBV is a major risk factor for HCC development. During HBV infection, the cellular immune response is thought to play a critical role in viral clearance and disease pathogenesis. Virus-specific CD8+ and CD4+ T cells play key effectors and regulatory roles in hepatitis B antiviral immunity (5). CD8+ T cells are the main effectors in the viral clearance of HBV. Chronic hepatitis is characterized by CD8+ T cell response unable to completely clear HBV from the liver, which consequently sustains continuous cycles of low-level cell destruction.

This results in a sustained immune response accompanied by liver injury and fibrogenesis. Over long periods of time, recurrent immune-mediated liver damage, regeneration and inflammation contribute to the development of cirrhosis and hepatocellular carcinoma.

Platelets are the smallest cellular components of human blood and, platelets adhere to the site of injury and aggregate with one another, a process known as primary haemostasis. In addition, during inflammation, platelets adhere to injury areas and facilitate the accumulation of cytotoxic T lymphocytes (CTLs) in the HBV infected liver (6). Therefore, earlier intervention of immune response can prevent liver damage by HBV infection. Reduction of prostaglandins and thromboxanes production by aspirin was through irreversible inactivation of the platelets cyclooxygenase (COX) enzyme which is expressed by cytokines, inflammatory stimuli, and some growth factors (7). The enzyme COX-1 produces thromboxane A-2 which necessary for platelet aggregation. For other drug, clopidogrel, it is an ADP-receptor P2Y12 inhibitor, which is required for stable platelets aggregation (8). Therefore, novel findings by Sitia *et al.* in PNAS provide new light on the pathogenesis of HBV-infected liver cancer, revealing a significantly effect of antiplatelet drugs in preventing its development (9). They used antiplatelet drugs to block indirect effect in animal model, the process of the chronic inflammation by HBV infection. On the other hand, previous study has indicated that the count of platelets at various stages of liver disease related to HBV has been determined. Patients with liver cirrhosis tend to

have lower platelet count while patients with HCC tend to have higher counts (10). Meanwhile, platelets may play an active and causative role during tumor angiogenesis (11). These suggest that platelets may play multiple roles in the process of tumor development. In addition, the direct effect of the virus itself, HBV viral proteins also play an important role in the process of HCC development such as HBX and HBsAg proteins (12,13). Therefore, it still can observe tumor formation after aspirin/clopidogrel treatment. Taken together, in this article, these results provide an important therapeutic strategy for prevention of HBV-induced HCC through immune-mediated necroinflammatory reactions by using antiplatelets drug.

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### References

1. Sherlock S, Fox RA, Niazi SP, et al. Chronic liver disease and primary liver-cell cancer with hepatitis-associated (Australia) antigen in serum. *Lancet* 1970;1:1243-7.
2. Kao JH, Chen DS. Changing disease burden of hepatocellular carcinoma in the Far East and Southeast Asia. *Liver Int* 2005;25:696-703.
3. Thorgeirsson SS, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet* 2002;31:339-46.
4. Feitelson MA, Sun B, Satiroglu Tufan NL, et al. Genetic mechanisms of hepatocarcinogenesis. *Oncogene* 2002;21:2593-604.
5. Yang PL, Althage A, Chung J, et al. Immune effectors required for hepatitis B virus clearance. *Proc Natl Acad Sci U S A* 2010;107:798-802.
6. Iannacone M, Sitia G, Isogawa M, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. *Nat Med* 2005;11:1167-9.
7. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. *Arterioscler Thromb Vasc Biol* 2004;24:1980-7.
8. Gachet C. Regulation of platelet functions by P2 receptors. *Annu Rev Pharmacol Toxicol* 2006;46:277-300.
9. Sitia G, Aiolfi R, Di Lucia P, et al. Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. *Proc Natl Acad Sci U S A* 2012;109:E2165-72.
10. Nwokediuko SC, Ibegbulam O. Quantitative Platelet Abnormalities in Patients With Hepatitis B Virus-Related Liver Disease. *Gastroenterology Research* 2009;2:344-9.
11. Pinedo HM, Verheul HM, D'Amato RJ, et al. Involvement of platelets in tumour angiogenesis? *Lancet* 1998;352:1775-7.
12. Diamantis ID, McGandy CE, Chen TJ, et al. Hepatitis B X-gene expression in hepatocellular carcinoma. *J Hepatol* 1992;15:400-3.
13. Hung JH, Teng YN, Wang LH, et al. Induction of Bcl-2 expression by hepatitis B virus pre-S2 mutant large surface protein resistance to 5-fluorouracil treatment in Huh-7 cells. *PLoS One* 2011;6:e28977.

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