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The association of HBV core promoter double mutations (A1762T and G1764A) with viral load differs between HBeAg positive and anti-HBe positive individuals: A longitudinal analysis – Reply

To the Editor:

Pan et al. [1] have expressed two concerns regarding our study. First, although no study subjects received antiviral therapy during the period of follow-up, some individuals may have been treated prior to the study. The members of the Long An cohort are low-income agricultural workers unlikely to be able to afford antiviral drugs, and none reported their use when questioned specifically at recruitment. Even if a few individuals had received therapy previously, their viral loads should have rebounded after the end of treatment and the longitudinal analysis carried out ensured that our results would not have been influenced. Furthermore, the differential effects of BCP mutations on viral load in HBeAg-positive and in HBeAg-negative patients have been reported by other investigators [2]. The strength of our study lies in the longitudinal analysis.

Their second point is that other factors, such as age, sex and viral genotype, may have influenced the viral loads. As stated in the methods Section 2.7.1 'Cross-sectional analysis', multiple linear regression analysis was used to assess whether any differences detected remained significant after adjusting for HBeAg status and those specific factors [3]. That was the case, although, for reasons of brevity, those analyses were not detailed in the paper. We do not consider that either of these issues compromises our findings.

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The retroviral myth of primary biliary cirrhosis: Is this (finally) the end of the story?

To the Editor:

The retroviral story of primary biliary cirrhosis (PBC) has been enriched by a new episode in the March issue of this Journal. In their article, Johal and colleagues report their study of a large number of liver samples taken from patients affected by

chronic liver diseases of all etiologies (including 26 PBC cases), at different stages, with or without hepatocellular carcinoma [1]. In all these samples, molecular methods were utilized to determine the presence of the mouse mammary tumor virus-like virus (coined MMTV-LV). There was no evidence of MMTV-LV env protein in healthy liver tissues while a variable proportion of samples with different chronic diseases manifested the presence of the virus. This proportion (namely 3/26 for PBC) did not differ among different etiologies, between early and advanced stages, or between neoplastic and non neoplastic tissues. While we welcome a new group in the dichotomy which has characterized the retroviral hypothesis of PBC, we feel the necessity to raise some concerns on the data and their interpretation.

The involvement of a retrovirus in the etiology of PBC was first proposed 11 years ago by Andrew Mason's group [2] and has since been supported by publications coming only from that group. This work has more recently culminated in a pilot trial for antiretroviral therapies in patients with PBC in which putative non validated endpoints (such as upper abdominal pain) were included [3]. In 2004, we undertook an unbiased and blinded effort to determine the presence of multiple MMTV molecular and tissue markers in a large number of fresh liver and peripheral blood cells from patients with PBC. We failed to identify any proof of MMTV [4]; we note that Johal et al. failed to cite subsequent editorials. Furthermore, we submit that the work by Johal and colleagues has fatal and naive flaws and does not address crucial questions arising from their results.

First, while stating that contaminations were carefully avoided, the authors utilized both paraffin-embedded and fresh liver tissues for DNA extraction, thus including an obvious source of potential contamination. Second, it is not established that the molecular methods used have adequate sensitivity for MMTV detection and sufficient specificity since sequencing was performed in a minor group of positive cases. Third, the number of healthy controls is clearly too limited to allow powerful comparisons given the rarity of the virus in PBC samples. Fourth, the authors have not attempted to explain the basis for the discrepancies between the findings from the three groups, including ours. Fifth and most importantly, the lack of association between etiology, stage, or cancer fails to identify any possible working theory behind the reported experimental observation. There is still no biologic or immunologic plausibility. The involvement of MMTV appears to be common to all chronic liver diseases in minor percentages and this clearly does not allow to formulate a rational hypothesis to recapitulate the observation, as suggested by experts in the field of autoimmunity [5].

For all the aforementioned reasons, we conclude this letter with the same conclusion we arrived at in 2004 [6]. The retroviral story for PBC has been around for almost a decade and no group has reproduced the original data nor developed any biologic plausibility. We are all working together for the common goal of improved patient care. But let us remind the readership of a saying attributed to Confucious: "Learning without thought is labor lost. Thought without learning is perilous".

References

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