Editorial: betaretrovirus in biliary epithelia of patients with autoimmune and cryptogenic liver disease – authors' reply

W. Wang*, S. Indik†, G. K.-S. Wong*,‡,§,¶ & A. L. Mason*,¶

*Center of Excellence for Gastrointestinal Inflammation and Immunity Research, University of Alberta, Edmonton, AB, Canada.
†Department of Virology, University of Veterinary Medicine, Vienna, Austria.
‡Department of Biological Sciences, University of Alberta, Edmonton, AB, Canada.
§BGI-Shenzhen, Bei Shan Industrial Zone, Shenzhen, China.
¶Li Ka Shing Institute of Virology, University of Alberta, Edmonton, AB, Canada.
E-mail: andrew.mason@ualberta.ca

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We thank Tabibian and Lindor for their comments on our article.[1, 2] There are multiple challenges for establishing a pathogenic role for human betaretrovirus (HBRV) in primary biliary cirrhosis (PBC). Immune-based diagnostics are clearly required for conducting large-scale epidemiological studies, for example. Also, methods to measure low-level viral infection are necessary to link clinical improvement with diminished viral load in clinical trials of combination anti-viral therapy in PBC.[3] Digital droplet PCR has shown promise in this area but linker-mediated PCR and next generation sequencing methods used in this study are too expensive and cumbersome.[2]

The concern that HBRV infection may just be an epiphenomenon is lessened somewhat by the association of viral infection with the mitochondrial phenotype observed in patients with PBC. The aberrant mitochondrial protein expression in virally infected biliary epithelium and lymph nodes has been documented in PBC patients[4] and mouse models of autoimmune biliary disease.[5]

We agree that genetic susceptibility is probably a major factor that impacts on the development and extent of disease following infection. Indeed, the related agent, mouse mammary tumour virus (MMTV) is associated with a variety of inflammatory and neoplastic disorders in mice (lymphoma, breast and renal cancer) manifesting in different genetic backgrounds.[5] Of relevance to detecting HBRV in normal individuals, diverse strains of mice have developed various mechanisms to control MMTV infection. For example, I/LnJ mice produce robust and sustained interferon-γ responses following MMTV infection and make neutralising antibodies that prevent viral spread.[6] This may be of relevance to the viral hypothesis of PBC, as many genes within the IL-12 axis upstream of interferon-γ production have been implicated in genome--wide association studies as providing risk for the development of disease.[7] Thus, further examination of the interaction of betaretrovirus infection with specific disease associated alleles is warranted to provide mechanistic insight how HBRV may become pathogenic in PBC patients.

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