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Microbes as trigger for Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis.

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Based on an interesting report (1) on an association between a retrovirus and primary biliary cirrhosis (PBC), where virus-like particles were demonstrated in cultured cholangiocytes from hepatectomy specimens, Poupon and Poupon (2) emphasized the need for a clinical trial with antiretroviral agents for patients with PBC. In this report, reverse transcriptase PCR and immunochemistry on lymph-node samples were employed to show a retrovirus infection in 73% of patients with PBC compared to 20% of controls. The retrovirus was related to the murine mammary tumour virus which is similar to the human β -retrovirus. The authors speculated how retrovirus and other viruses may trigger autoimmune reactions leading to PBC. Selmi *et al.* (3) were, however, unable to confirm a role of retrovirus in PBC.

We earlier reported that patients with PBC, primary sclerosing cholangitis (PSC) (4) and hepatocellular carcinoma (HCC) (5) but not with liver metastases from colonic carcinoma often (75%, 92%, 75%, and 3%, respectively) were positive for *Helicobacter* DNA in liver biopsy specimens. *Helicobacter* species 'liver' DNA with high similarity in the 16S rDNA to *H pylori* was detected in patients with HCC (6), and later isolated from the liver of a patient with cirrhosis and chronic liver disease (7). Analysis of *H pylori* DNA of liver tissue showed that significantly more patients with HCC and cholangiocarcinoma (13/34, 33%) harboured *H pylori* cagA DNA than patients with liver metastases from colorectal carcinoma (3/20, 15%) ($p = <0.05$; Nilsson H-O, in preparation). *Helicobacter* species-like spiral- and coccoid-shaped organisms were demonstrated in Kupffer cells of a patient with PSC by immune electron microscopy (IEM)(8). By analysing the immune response to *H pylori* and to some enteric *Helicobacter* species by Western blot we demonstrated specific immune response to various *Helicobacter* cell surface proteins in patients with PBC, PSC, and autoimmune hepatitis in studies in Estonia (9) and Southern Sweden (10), as well as in patients with chronic cholecystitis in Ukraine, also using PCR and IEM (11).

These findings add to the growing list of microorganisms detected in the hepatobiliary tract of patients with chronic infections and malignancies in these organs. Already in 1989, anti-Lipid A antibodies to various *Escherichia coli* rough forms were reported in the liver of patients with PBC (12). This finding has later been followed by reports on *Chlamydia pneumoniae*, *Mycobacterium gordonae*, *Novosphingobium aromaticivorans* and other bacteria (13-15). Also *Cryptosporidium parvum* has been reported to be associated with sclerosing cholangitis (16). PBC is an autoimmune disease, and several of the cited studies report reactivity to pyruvate dehydrogenase, PDC-E2 (17). *N aromaticivorans* PDC-E2, particularly, but also that of *M gordonae* and other bacterial species have a high degree of homology to the immunodominant region of human PDC-E2. *H pylori* induces autoantibodies reactive with a protein in gastric parietal cell canaliculi, and *H hepaticus* induces heat shock protein (Hsp) 70 in hepatitis in mice, with homology to human Hsp 70 (18,19). These data provide a basis for molecular mimicry, i.e. that microbial molecules contain epitopes which cross-react with molecules in human, especially mitochondrial antigens.

Subclinical or overt infections with different microbial agents appear to induce autoantibodies. This is characteristic of PBC. We propose systematic studies on antibodies to microbial antigens in various forms of chronic hepatobiliary diseases to be carried out in different geographic locations, parallel to microbial detection in the gastrointestinal tract. It

seems possible that antigens from dissociated microbes in Kupffer cells, macrophages and lysed cells can trigger autoimmune-like phenomena in PBC and PSC as a result of past clinical or subclinical infection.

Conflicts of interest.

None

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