



# Serum extracellular vesicles—a promising path towards an individualized medicine in primary sclerosing cholangitis and related cholangiocarcinoma

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Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of the biliary tract system, whose mechanisms of pathogenesis remain elusive. Most importantly, PSC is considered a major medical burden due to its premalignant nature (1). Malignant complications in PSC frequently occur within the hepatobiliary system, arising predominately as cholangiocarcinoma (CCC) (2). The overall risk for PSC patients developing biliary tract cancer throughout their life is estimated to be around 13% to 14% or even up to approximately 30% in some cohorts (1,3,4). Due to its progressive and destructive inflammation of the bile ducts, PSC patients are frequently in need of liver transplantation. The average time span from diagnosis to liver transplantation is around 12 years (5).

Although not a classical malignant complication of PSC, some authors discuss an increased risk for hepatocellular cancer (HCC) in PSC patients (6). Thus, in a newly diagnosed tumor of the liver, HCC has always to be considered in differential diagnostic procedure.

PSC patients commonly present with late stage biliary tract cancer (1). Moreover, half of all PSC patients have hepatobiliary tract malignancies already at the time of their PSC diagnosis (7). Thus, a major challenge is the ability to screen for CCC. However, the diagnosis of PSC and concomitant CCC is difficult due to the lack of minimally invasive screening tests, such as detection of a biomarker in serum, and due to the lack of decisive identification of PSC patients at high risk for CCC.

The last decade's predominant approach to personalize PSC medicine was through genotyping. However, genotype-phenotype association data on clinical outcomes are often inconsistent and not applicable for a majority of disease situations and patients (8). Genotypic studies in PSC have helped advance our understanding of its pathogenesis and classification, but its utility for diagnosis and risk assessment remain poor (9). Risk factors for hepatobiliary cancer in PSC, including long history of inflammatory bowel disease (IBD), male gender, and smoking are of only minor help identifying individuals at risk for PSC (7). There remains a lack of prognostic tools available for clinical application to determine an individual's PSC risk (10).

The etiology of PSC is still unknown; however, PSC is closely associated with immune related disorders such as IBD or autoimmune hepatitis as well as co-existing autoantibodies suggest that PSC is an immune-mediated disease (4,11). As such, PSC-associated seromarkers have been evaluated as diagnostic and prognostic markers of disease. In fact, we recently observed an association of the pancreatic autoantibody against glycoprotein 2 (anti-GP2) with the development of CCC and poor survival in two independent PSC cohorts (12). Anti-GP2-IgA is a highly promising biomarker to identify PSC patients at risk for progression and development of CCC. The only other serological autoantibody with comparable prevalence is p-ANCA, however, clinical correlations with p-ANCA remain inconsistent across more than 20 studies performed (11).

A highly promising new approach to improve diagnostic procedures and to identify an individual's risk for CCC, HCC, and PSC is reported by a Spanish team of researchers with collaborators from Germany, Poland, and Italy (13). Arbelaiz *et al.* isolated serum extracellular vesicles (EVs) from patients with PSC, CCC, HCC, and healthy controls. EVs have a lipid bilayer and are between 40 and 1,000 nm in size. They are generated by diverse cell types and contain specific proteins, lipids, RNA, DNA, or metabolites (13-15). Exosomes are a prominent example of an EV. Released into circulation, EVs are present in biological fluid and take part in intercellular communication. EVs' easy accessibility has made them attractive options for diagnostic purposes. The work by Arbelaiz *et al.* indicate that EVs may be of diagnostic value for PSC diagnosis as well as for detection of hepatobiliary malignancies in PSC. The authors demonstrate that the protein content of EVs was significantly higher in the studied HCC patients than in PSC or CCC patients, which may allow to distinguish hepatic from biliary cancer. Moreover, the analyzed EVs were predominantly identified as exosomes. Proteome profiling of these exosomes identified several differentially expressed proteins between the groups. With a considerably high diagnostic value, (I) patients with HCC could be differentiated from healthy controls as well as from intrahepatic CCC, (II) PSC with and without cirrhosis could be discriminated from controls, and (III) CCC in late but also early stages was discriminated from PSC without cancer, something of high clinical value. Finally, orthotopic implantation of CCC human cells into livers of immunodeficient mice resulted in the release of EVs with similar protein profiles, suggesting the disease specificity of these identified EVs.

Arbelaiz *et al.* nicely demonstrate in a proof of concept manner that assessing proteomic signatures in serum EVs could be a promising diagnostic tool for PSC and related hepatobiliary cancer in order to tailor medical management and personalize individual care in PSC. Future directions of EV research in PSC should therefore include larger cohorts and the combination of other PSC related biomarkers such as autoantibodies, gut microbiome composition and metabolic signatures. This will allow the segregation of the heterogeneous PSC population and drive targeted and personalized approach to PSC care towards precision medicine. Finally, this will allow us not only to optimize our surveillance strategies but will give us a deeper insight into the pathology of the disease towards the development of additional personalized therapies.

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