Editorial

sVAP-1: a novel potential therapeutic target and marker for risk stratification in primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a chronic condition affecting the liver, targeting mainly intra- and extra-hepatic biliary ducts, potentially able to evolve to cirrhosis, biliary cancer and liver failure (1). Lack of understanding of its pathogenesis is likely to be one of the main reasons why there is still no effective treatment besides liver transplantation.

PSC is strictly connected with inflammatory bowel disease (IBD), since the majority (>80%) of western patients have concomitant IBD (2). Therefore, researchers have focused on the potential link between gut and liver, the so-called "gut-liver axis" (3). The main hypothesis underlying gut-liver axis theory starts from a few physiological considerations: the liver is involved in immunosurveillance and tolerance towards antigens coming from the gut, so it is naturally influenced by changes in the intestinal microenvironment. In genetically-predisposed individuals dysbiosis can be the trigger leading to activation of innate immunity and effectors T cells, with subsequent local inflammation, a scenery well described in IBD pathogenesis. A leaky intestinal barrier may allow bacterial translocation to the liver, where, in turn, activation of pattern recognition receptors may induce initiation of inflammation cascade (4). Mucosal T cells effectors can be recruited through homing signals expressed by intestinal endothelium, like mucosal address in cell adhesion molecule (MAdCAM-1) and Chemokine ligand 25 (CCL25) (5). Under normal circumstances, MAdCAM-1 is expressed in the gut but not in the liver, while in PSC patients MAdCAM-1 is aberrantly expressed also in the liver (6). Its expression is upregulated by an adhesin, VAP-1, that, conversely, does have a peculiar specificity for the liver. Being an amine oxidase, VAP-1 can also process amine substrates generated by gut microbes, and the higher the number of substrates the more VAP-1 upregulates its enzymatic activity (7).

Trivedi and coauthors have recently published an elegant translational article where they measured VAP-1 in healthy donor livers and in the liver of end stage patients with autoimmune liver diseases, analysed its activity, dosed its soluble form and correlated serum levels of soluble VAP-1 (sVAP-1) with clinical outcomes (8).

They have shown how VAP-1 expression is increased in the liver of patients with autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and PSC, with a peculiar staining through fibrotic nodules. The greatest levels of VAP-1 mRNA are found in PSC and, consistently, enzymatic activity is increased in PSC liver, and this is evident not only in comparison to healthy liver but also to AIH and PBC samples.

Then they better characterized the ability of VAP-1 to help $\alpha4\beta7^+$ T lymphocytes to adhere to the hepatic endothelium. In this paper, they have shown that this binding process can be stimulated by enzymatic activity of VAP-1 and be inhibited by a selective VAP-1 inhibitor. Even though it is still matter of speculation whether VAP-1 amine substrates are produced locally or come from the inflamed

gut, the amine oxidase activity is substrate-dependent, with the maximum efficiency with cysteamine, a substance that can be generated both by the colonic epithelium and by gut microbes (9).

Taken altogether, these findings add a piece of evidence to the pathogenetic model of an inflamed and dysbiotic gut where $\alpha 4\beta^{+}$ T lymphocytes are activated and then recruited to the liver, with VAP-1 playing the role of enhancer of this recruitment via its action on adhesins like MAdCAM-1.

There are preliminary data from a murine model of AIH about therapeutic efficacy of anti-VAP-1 on liver biochemistry and histology by blocking the recruitment of CD4 lymphocytes (10). And a phase II study to determine the safety and preliminary efficacy of a human monoclonal antibody (BTT1023) targeting VAP-1 in patients with PSC is currently ongoing (11).

Trivedi and coauthors subsequently measured serum concentrations of soluble VAP-1 from blood samples of patients with PSC, AIH, PBC, IBD alone and healthy volunteers, finding higher values in PSC patients than other groups. However, before concluding that VAP-1 can be a disease-specific biomarker we should consider that PSC cohort was made by more advanced cases. sVAP-1 levels were higher in cirrhotic patients (even though it was not able to differentiate between compensated and decompensated ones) and, moving back to the histological samples analysis, this agrees reasonably with the high expression in fibrous areas and αSMA-positive cells. There were not significant correlations with liver function tests expressed as continuous variables (except for platelets), but sVAP-1 was able to predict transplant-free survival, and this was true even when analysis was restricted only to those with cirrhosis or, on the other hand, with normal serum bilirubin, albumin or platelets.

Therefore, in view of the need for biomarkers in a difficult-to-predict disease like PSC (12), authors raise the possibility that sVAP-1 might help clinicians to better stratify patients with advanced PSC. In order to validate results obtained with immunofluorometric assay, they performed a chemiluminescence assay and confirmed this predictive role on their samples and on samples of PSC patients from a Norwegian cohort.

However, we are still far from having a biomarker available in daily practice or for clinical trials: cut off levels between the two techniques were different, sVAP-1 needs validation on a bigger cohort of patients and we still do not know at which point of the natural course of the disease sVAP-1 starts rising its values. In addition, the unpredictable clinical nature and the absence of a treatment makes risk stratification in PSC a multi-modal process, i.e. all the different available predictors should be taken together (12).

To conclude, Trivedi and colleagues have further elucidated gut-liver axis pathway in an orphan disease like PSC, potentially providing either a novel potential biomarker and/or a target for future therapies.

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