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Serological biomarkers for the management of primary sclerosing cholangitis

Tornai D *et al*. Serological biomarkers of PSC

David Tornai, Peter Laszlo Ven, Peter Laszlo Lakatos, Maria Papp

Abstract

Clinical manifestations and progression of primary sclerosing cholangitis (PSC) are heterogeneous, and its pathogenesis is poorly understood. Importance of gut-liver interaction in the pathogenesis has been clinically confirmed and highlighted in the different theories. Recent advances regarding biomarkers of biliary-gut crosstalk may help to identify clinically relevant PSC subgroups assisting everyday clinical work-up (*e.g.,* diagnosis, disease stratification or surveillance) and the exploration of potential therapeutic targets. Alkaline phosphatase produced by the biliary epithelium is consistently associated with prognosis. However, its level shows natural fluctuation limiting its use in individual patient. Inflammatory, cell activation, and tissue remodeling markers have been reported to predict clinical outcome. Elevated Immunoglobulin (Ig) G4 level is associated with shorter transplantation-free survival. IgG type atypical perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCAs) are non-specific markers of various autoimmune liver diseases and may reflect abnormal B-cell response to gut microbial antigens. IgG type atypical P-ANCA identifies PSC patients with particular clinical and human leukocyte antigens genetic characteristics. Presence of IgA type anti-F-actin antibody (AAA) may predict progressive disease course, and it is associated with enhanced mucosal immune response to various microbial antigens and enterocyte damage. IgA type anti-glycoprotein 2 (GP2) antibodies identify patients with severe disease phenotype and poor survival due to enhanced fibrogenesis or development of cholangiocarcinoma. Elevated soluble vascular adhesion protein-1 (sVAP-1) level is associated with adverse disease outcomes

in PSC. High sVAP-1 levels correlate with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expression in the liver that contributes to gut activated T-cell homing to the hepatobiliary tract. In the present paper we review the evidence on these possible serological markers potentially helpful in filling the unmet clinical needs in PSC.

Key Words: Primary sclerosing cholangitis; Hepatobiliary; Serological biomarker; Immunoglobulin; Inflammatory; Tissue remodeling

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Core Tip: Recent advances in biomarker research may help clinicians identifying relevant subgroups of primary sclerosing cholangitis (PSC) and assist everyday clinical work-up. However, a diagnostic biomarker is still an unmet need. On the other hand, several biomarkers have been reported to predict outcome in PSC, however most of them have not been validated by subsequent studies. IgA type anti-glycoprotein 2 antibody is the first one to be supported by a satisfactory number of clinical studies and could be incorporated into clinical practice. These discoveries also reveal different aspects of PSC providing with potential therapeutic targets.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic and progressive inflammatory disease of the bile ducts leading to the formation of intermitting bile duct strictures and dilatations, with periductal fibrosis that in most cases progresses to cirrhosis and decompensated disease stage. Moreover, PSC is associated with the development of cholangiocarcinoma (CCA) and colorectal cancer[1]. The etiology of PSC is poorly understood. However, the gut-liver interaction seems to be a driving factor in its development. It has been hypothesized that the interaction of the gut microbiome and certain genetically determined factors [such as certain human leukocyte antigens

(HLA)] leads to the development of disrupted immunological pathways, as a result of an autoimmune reaction to yet unknown antigen(s). Most abnormalities discovered by genetic studies support a disruption of T cell functions. Gut-derived antigens significantly induce antigen presentation by major histocompatibility complexes (MHCs) on the surface of antigen-presenting cells to T cells, which, following clonal expansion, can be delivered to both the intestinal tract and the liver[2]. Abnormal T cell activation results in increased release of various cytokines [such as transforming growth factor-β (TGF-β)] involved in the development of fibrosis. Activation of B cells is indicated by the frequent appearance of bacterial translocation (BT) related serological antibodies [*e.g.*, anti-neutrophil cytoplasmic antibodies (ANCAs)].

The diagnosis of PSC is difficult, no biomarker specific to the disease has been identified so far. In the presence of chronic cholestasis, the diagnosis is based on magnetic resonance cholangiography (MRCP) or, much less frequently today, endoscopic retrograde cholangiopancreatography (ERCP) with confirmation of biliary lesions and strictures. Careful exclusion of known causes of secondary sclerosing cholangitis (SSC) is also necessary. Immunoglobulin (Ig) G elevation and the presence of atypical perinuclear ANCA (P-ANCA) in serum are common but are not disease-specific serological alterations[3]. Routine liver biopsy is no longer routinely performed in the diagnosis of PSC and is only necessary in suspected cases of small duct PSC, when the cholangiogram is normal, or to confirm overlap syndrome with autoimmune hepatitis.

The disease course of PSC is variable. There are a few promising biomarkers to predict disease activity and progression, yet almost none has been validated in subsequent studies. A recently discovered serological biomarker [IgA type antibodies against pancreatic glycoprotein 2 (anti-GP2 IgA)][4,5] is the first that has a predictive value in PSC confirmed in multiple studies[6,7]. However, it has not been integrated into clinical practice. Consequently, the question of accurate risk assessment, disease stratification and follow-up strategy for patients with PSC is still unresolved[8].

Studying biomarkers characterizing the dialogue between the biliary tract and the intestine in PSC may not only identify clinically relevant subgroups for disease stratification, but can also unravel new pathogenesis-relevant correlations. This could in turn lead to the discovery of new therapeutic targets.

While biomarkers from other body fluids (*e.g.*, bile) can reveal important parts of the pathogenesis, blood is more readily available for clinicians and can be obtained in a highly controlled fashion (in contrast to *e.g.*, stool). This makes serological biomarkers the most appropriate for everyday clinical use, therefore these are the markers we focus on in this review.

ROUTINE LABORATORY TESTS AND COMPOSITE SCORES

Alkaline phosphatase

Various clinical studies have consistently reported a correlation between alkaline phosphatase (ALP) levels and disease progression, but its individual application is difficult. In PSC, the fluctuation pattern of ALP is different from that observed in primary biliary cholangitis, and the degree of elevation is influenced by the development of various biliary complications (cholangitis, gallstones or the appearance of a dominant stricture). Thus, it is not surprising that the ALP thresholds or values of change associated with disease outcomes in certain studies were not confirmed by other studies[9]. However, certain studies highlighted the importance of ALP fluctuation in CCA development free survival. The risk of developing CCA was significantly higher in patients with constantly high ALP levels without reduction[10-13]. Thus, further studies are needed to determine the significance of ALP level variation also in transplant free survival (due to progression of fibrosis) and treatment response.

Mayo risk score

In the absence of individual predictive markers, researchers tried to develop predictive models incorporating multiple markers. These scoring systems, however, also contain clinical parameters besides serological markers. The first and still the most widely used

clinical prognostic model is the mayo risk score (MRS), which, as modified in 2000, no longer includes invasive or subjective parameters[14]. Abnormal value of the factors included in the MRS [serum bilirubin, albumin and aspartate aminotransferase (AST) levels, and esophageal variceal bleeding], with the exception of age, represents advanced liver disease. Thus, the discriminatory potential of this scoring system is inadequate in the early stages of PSC. In addition, the predictable time period for disease progression is only around four years. The model was also not able to predict the adverse disease outcome associated to high-dose ursodeoxycholic acid treatment (28-30 mg/kg/d) either[15].

Amsterdam-Oxford model

The Amsterdam-Oxford model (AOM) is another prognostic scoring system for PSC[16], which includes seven objective parameters (PSC subtype, age at diagnosis, platelet count, serum albumin, ALP, AST and bilirubin levels). This scoring system was developed to overcome the limitations of MRS in the prediction of transplant-free survival. It can be used to estimate longer-term prognosis of PSC (15 years) and can be recalculated at a later timepoint. However, the discriminative power of the model was only moderate (C-statistic: 0.68). In contrast, it has the advantage of being much more widely applicable (the reliability of the model was consistent in the two populations and at different timepoints) as it was developed using population-based data rather than data from transplant centers.

UK-PSC scores

The UK-PSC scores were also developed to predict transplant-free survival[17]. Two models were created for 2-year and for 10-year prediction, derived from a cohort of 1001 PSC patients and validated in two independent cohorts adding up to 451 patients. The incorporated variables were serum bilirubin, ALP, albumin, platelets, presence of extrahepatic biliary disease, and variceal hemorrhage. "Both short- and long-term UK-PSC risk scores had better performance than MRS and AST-to-platelet ratio index when

predicting outcomes [C-statistics for 2-year survival (short-term) were 0.81 *vs* 0.75 and 0.63, respectively; for 10-year survival (long-term) were 0.80 *vs* 0.79 and 0.59, respectively]."

PSC risk estimate tool

PSC risk estimate tool (PREsTo) was developed to predict the advent of hepatic decompensation (ascites, variceal hemorrhage, or encephalopathy). The model was derived from data of a multicenter North American cohort and validated in an international multicenter cohort including 509 and 278 subjects, respectively. Individuals with advanced PSC or CCA at baseline were excluded. PREsTo incorporates nine variables: Bilirubin, albumin, serum ALP times the upper limit of normal, platelets, AST, hemoglobin, sodium, patient age, and number of years since the diagnosis of PSC. In predicting hepatic decompensation PREsTo performed better than model of end stage of liver disease (MELD) score and MRS (C-statistics: 0.9 *vs* 0.72 and 0.85, respectively)[18]. The equation is not provided, only an online calculator is available.

Enhanced liver fibrosis test

The enhanced liver fibrosis (ELF) test (Siemens ADVIA Centaur®) is based on purely serological measurements summarizing three direct components of fibrogenesis (hyaluronic acid, tissue inhibitor of metalloproteinase 1 and type III procollagen amino-terminal propeptide). It has been reported to be a strong predictor of prognosis (mortality, liver transplantation) in PSC independently of MRS. Validation of this result was successful in multiple studies (C-statistic: 0.79-0.81)[19,20]. In a recent study, the ELF score slightly increased in PSC patients over a 5-year follow up period and showed low intrapersonal variability supporting the consistency of this score[21].

IMMUNOGLOBULINS

IgG4

About 10% of patients have elevated serum IgG4 Levels without IgG4-associated disease. Recently, IgG4 determination is recommended at least once in all patients with PSC[22]. Elevated serum IgG4 levels (>140 mg/dL) in PSC patients were associated with higher values of liver function tests, higher MRS and shorter time to liver transplantation, which clearly indicates a more severe disease course in this subgroup of patients[23]. It is unknown whether the addition of a systemic glucocorticoid to treatment in the high IgG4 subtype of PSC may be beneficial in curbing disease progression[24].

ANCAs

Various other serum autoantibodies have been described in PSC patients, however, they are considered unspecific, since they may be present also in other diseases. The most frequently observed antibodies in PSC are ANCAs, but antinuclear antibodies and anti-smooth muscle antibodies were also reported to be frequently associated with PSC[25].

The occurrence of IgG isotype atypical P-ANCAs in PSC are common, up to 80% of cases. The putative role of intestinal bacteria in ANCA formation (homology between human beta-tubulin isotype 5 and bacterial FtsZ protein, molecular mimicry) has been described[26]. Early, small scale, case-control clinical studies[27] found no correlation between ANCA formation and clinical or genetic features of PSC. Hov *et al*[28], however, in a large comprehensive case-control study, demonstrated that risk genes with a strong association to PSC formation (HLA-B*08 and DRB1*03) were also associated with ANCA formation. Interestingly, association between presence of PSC related HLA alleles (B*08, C*07, and DRB1*03) and increased risk of acute rejection syndrome in liver transplant recipients has also been reported (while DRB1*04 was found to be a protecting factor)[29].

The antibody against serine proteinase-3 (PR3) is a type of cytoplasmic ANCAs (C-ANCAs). PR3-ANCA is typically observed in small vessel vasculitis[30] but recently has been reported in ulcerative colitis (UC)[31] that prompted researchers to investigate this antibody in PSC as well. Interestingly, in the setting of PSC, PR3-ANCA seems to be

associated with worse liver biochemistry rather than with a co-diagnosis of UC[32]. In the recent study by Wunsch et al[7], besides worse liver function tests and MELD score, PR3-ANCA has been shown to be associated with CCA development (HR = 9.8, 95%CI = 1.3-74.5; P = 0.03) and risk of shorter transplant free survival (HR = 1.8; 95%CI = 1.3-2.8; P = 0.01). However, the predictive capacity of PR3-ANCA was not confirmed in the validation cohort where the frequency of PR3-ANCA was found to be surprisingly low (5% in contrast to 54% in the discovery cohort) and CCA development was also less prevalent[7].

IgA type autoantibodies

IgA is the most important immunoglobulin isotype involved in mucosal immunity[33]. Since the gut-liver interaction plays a central role in the pathogenesis of PSC, the formation of IgA type autoreactive antibodies is a characteristic feature of the disease. Under physiological conditions, monomeric IgA in serum inhibits immunological processes (so-called immunosuppressive effect). However, in pathological conditions, immune complexes formed by aggregation of monomeric IgA molecules can activate immunological processes by binding to myeloid cells[34]. IgA, produced by plasma cells lining the gut and biliary epithelium, is a highly abundant immunoglobulin in bile and plays a central role in the defense against intestinal pathogens. Biliary epithelial cells (that are the cellular targets of injury in PSC), and intestinal epithelial cells transport the IgA molecules into the biliary and intestinal lumens, respectively (→secretory IgA)[35-37]. However, in the past, most studies on serological antibodies in autoimmune liver diseases, like in the case of ANCA, have focused mainly on IgG isotype antibodies, and the IgA isotype is only recently gaining attention[38].

The work of Berglin et al[39] is an example, which highlighted the described importance of IgA isotype antibody related pathogenetic pathways in PSC. They demonstrated that in the presence of IgA isotype autoantibodies against biliary epithelial cells, disease progression was faster than in their absence. No similar correlation was observed for IgG isotype antibodies.

In 2015, our group reported the association between PSC and the presence of anti-GP2 IgA antibodies in inflammatory bowel disease (IBD) patients[40]. Subsequently, anti-GP2 IgA positivity was demonstrated being able to predict a progressive disease course in PSC by our and another group[4,5]. These results were confirmed later by further studies[6,7]. In total, 1111 PSC patients have been evaluated for the presence of anti-GP2 IgA and prevalence was found between 30.8% and 52.2%[8]. Anti-GP2 IgA was consistently reported to be associated with a more severe PSC phenotype with a 2- to 5-fold higher risk to develop end stage liver disease with a need for liver transplantation (Figure 1). Consequently, anti-GP2 IgA may soon be integrated into clinical practice for risk assessment in PSC. Moreover, anti-GP2 IgA can also identify a subset of PSC patients with existing biliary tract cancer or with increased risk for developing it during the disease course. This association between anti-GP2 IgA and CCA was reported by Jendrek *et al*[4] and confirmed by Wunsch *et al*[7] both evaluating two cohorts each, providing strong evidence that incorporation of anti-GP2 IgA into CCA surveillance protocols could be beneficial (Figure 1).

IgA autoantibody against F-actin has been also reported being associated with enhanced mucosal immune response to various microbial antigens and enterocyte damage in PSC, and to identify PSC patients with progressive disease (HR = 4.54; 95%CI = 1.14-18.18; *P* = 0.032)[41]. Cytoskeletal F-actin initiates an extracellular damage-associated molecular pattern signaling pathway through DNGR-1/CLEC9A and Syk-SFK that results in antigen cross-presentation to CD8+ T cells[42–45]. CD8+ T cells, after activation in the gut, can be recruited to the liver and induce immune-mediated cholangitis in mice[46].

OTHER SEROLOGICAL BIOMARKERS

Interleukin-8

As a result of increased lipopolysaccharide (LPS) exposure, biliary epithelial cells produce interleukin-8 (IL-8), which has a proliferation-promoting effect and enhances fibrogenesis gene expression. In the study by Vesterhus *et al*[47], using modern antibody

array technology, elevated serum IL-8 showed the strongest association with poor transplant-free survival among pro-inflammatory markers. However, the predictive values of MRS and ELF test for clinical outcomes were found to be higher than that of IL-8.

Macrophage activation markers

Bossen *et al*[48] found that macrophage activation markers, soluble CD163 (sCD163) and mannose receptor (sMR), were increased according to disease severity in 2 independent PSC cohorts of 138 and 159 patients. In both cohorts, sCD163 and sMR levels raised parallel with increasing liver enzymes, MRS and ELF test. Patients with high baseline levels of sCD163 (> 3.86 mg/L) had decreased transplant-free survival during the 8-year follow up in both cohorts (35.2% *vs* 83.0% in the combined cohort). sMR showed similar association only in one of the cohorts with more severe disease features. In Cox regression, sCD163 also performed better in the more severe cohort (HR = 3.15 and 2.89) but it lost significance in the multivariate model against ELF test and AOM score.

BT markers

In a study investigating serum markers of BT, serum levels of zonulin, intestinal fatty acid binding protein, soluble CD14 (sCD14), LPS and LPS-binding protein (LBP) were measured in 166 PSC patients and 100 healthy controls[49]. LBP and sCD14 Levels were higher, whilst zonulin levels were lower in PSC patients compared to controls. This latter difference disappeared with the exclusion of PSC patients with elevated prothrombin time (indicating advanced liver disease). In patients with CCA, sCD14 Levels were higher compared to patients without it. High sCD14 and LBP values (> 1638 ng/mL and > 13942 ng/mL, respectively) were associated with reduced transplantation-free survival independently of MRS (HR = 2.26; 95%CI = 1.15-4.43; *P* = 0.018 and HR = 2.00; 95%CI = 1.17-3.43; *P* = 0.011, respectively). Further studies are needed to validate these findings.

Extracellular remodeling markers

In a cohort of 138 Large-duct PSC patients (74% with IBD) using 52 UC patients as controls, Nielsen *et al*[50] investigated the predictive potential of 4 extracellular remodeling markers related to collagen formation (PRO-C3 and PRO-C5) and collagen degradation (C3M and C4M). All markers were elevated in PSC compared to UC patients, with PRO-C3 showing the most robust difference. High serum levels of three markers (with the exception of C3M) were associated with shorter transplant-free survival during a 4-year follow up period. In the univariate Cox regression model (using tertiles of the markers) PRO-C3 had the highest hazard ratio (HR = 3.02; 95%CI = 1.96-4.67, $P < 0.001$) but it failed to predict survival in the multivariate model including ELF test, while PRO-C5 remained an independent predictor (multivariate HR = 1.92; 95%CI = 1.28, 2.88; $P = 0.002$). The combination of PRO-C3 and PRO-C5 resulted in significantly improved odds ratio (OR = 47.3; $P < 0.001$) compared to the individual markers and ELF test. However, in this latter test, the authors compared the outcomes associated with the first (lowest) tertile of the markers to those associated with the third (highest) tertile. Further studies are needed to confirm the importance of these findings as well.

MicroRNA-122

MicroRNA-122 (miR-122) is the most abundant microRNA in the liver, orchestrating molecular pathways in hepatocytes and regulating liver functions including lipid and cholesterol homeostasis. MiR-122 deficiency leads to inflammation, cholestasis and ultimately fibrosis of the liver[51]. Friedrich *et al*[52] investigated the predictive potential of miR-122 in 114 PSC patient with prospective follow up of 10 years. They divided the population to patients with low and high miR-122 levels based on the median value of the marker (CT-value of 28.5). Low miR-122 levels were associated with higher risk of death or need for liver transplantation (HR = 1.27; 95%CI = 1.04-1.39; $P = 0.009$) even in the multivariate Cox regression model including MRS, presence of dominant stricture and IBD (HR = 1.19; 95%CI = 1.00-1.43; $P = 0.045$).

Soluble vascular adhesion protein 1

Expression of vascular adhesion protein 1 (VAP-1) and amine oxidase enzyme activity in the liver endothelium are increased in PSC. The former results in an elevation of its soluble form (sVAP-1) in patients' sera. Elevated levels of sVAP-1 (> 529 ng/mL) in PSC are associated with an adverse disease outcome, independent of the presence of cirrhosis (HR = 3.85; 95%CI = 1.57 to 9.34; P = 0.003)[53].

Increased VAP-1 activity results in the expression of mucosal addressin cell adhesion molecule (MAdCAM-1) in liver tissue, which is otherwise expressed only in the intestinal endothelium. MAdCAM-1 binds to α4β7 integrin receptors on effector T lymphocytes, which is required for lymphocyte homing. Thus, abnormally expressed MAdCAM-1 in the liver results in the entry of gut activated effector T lymphocytes into liver tissue[53]. The increased expression and intrahepatic activity of VAP-1 may be attributed to the altered intestinal flora and the increased amine influx into the portal tract due to the inflamed, permeable bowel. The pathological amine substrate of VAP-1 is cysteamine[53], which causes colitis and colorectal carcinoma in mice. The Escherichia genus, which is able to produce cysteamine *in vitro*, is upregulated in the mucosa-associated microbiota population in PSC. However, the intestinal epithelium itself is capable of cysteamine production *via* the ectoenzyme vanin-1. The observation that cysteamine enhances colonic inflammation and carcinogenesis is consistent with the increased colon carcinoma formation observed in PSC. The aldehyde derivative formed during the metabolism of cysteamine causes abnormal collagen cross-binding, which could theoretically contribute to increased fibrogenesis. Increased VAP-1 activity in liver and colonic tissue is most likely an attempt to counteract the increased amine load resulting from colitis.

The newly discovered VAP-1 pathway is one explanation of how colitis and increased amine production lead to damage of liver tissue. VAP-1 may be a potential therapeutic target in the future due to its effect in promoting α4β7/MAdCAM-1 interaction. A

VAP-1 antagonist may also be able to regulate the migration of effector T lymphocytes from the inflamed intestine to the liver and thereby inhibit fibrogenesis[53].

The biomarkers used individually or as parts of score systems are summarized in Figure 2.

SEROLOGICAL BIOMARKERS FOR DETECTING CHOLANGIOCARCINOMA IN PSC

Carbohydrate antigen 19-9 (CA19-9) is the most commonly used serological marker for screening CCA, but its application is limited in PSC by the lack of comprehensive studies comparing PSC patients with and without CCA. Most studies were too small and ultimately provided inconsistent cut-off values[54]. A recent development in this field is the discovery of the role of fucosyltransferase (FUT) 2 and 3 in influencing the serum levels of CA19-9 in patients with PSC. These enzymes catalyze the final steps of CA19-9 biosynthesis. The study identified FUT genotypes with low, inter-mediate, and high CA19-9 synthesis capacity displaying distinct CA19-9 serum levels[55]. According to these data, CA19-9 is not an appropriate marker for CCA screening in patients with a low CA19-9 biosynthesis genotype since they do not synthetize CA19-9. This group can be identified by a Lewis-negative blood group which is also determined by these enzymes. In contrast, the high CA19-9 biosynthesis genotype might be a reason for false positive results[55]. In addition, bacterial cholangitis can be another explanation for increased CA19-9 Level in PSC patients without CCA[56].

Finally, a study demonstrated a significant influence of FUT2 genotype also on CEA serum levels. The most prominent effect was observed in the subgroup incapable of CA19-9 biosynthesis[57]. Studies with other serological biomarkers, like angiopoetin-2[58] or cytokeratin fraction 21-1[59] have not reached satisfactory results in terms of identifying individuals with CCA among PSC patients.

CONCLUSION

Several promising discoveries have been made on biomarkers for PSC. The first validated prognostic biomarker (anti-GP2 IgA) is finally ready to be incorporated into clinical practice, and the investigations highlighted important pathophysiological mechanisms for future research that might open new avenues for medical therapy. However, we still lack specific serological markers that could support the diagnosis of PSC. Additionally, a serological marker with satisfactory discriminative power to aid the recognition of CCA in PSC patients is another unmet need.
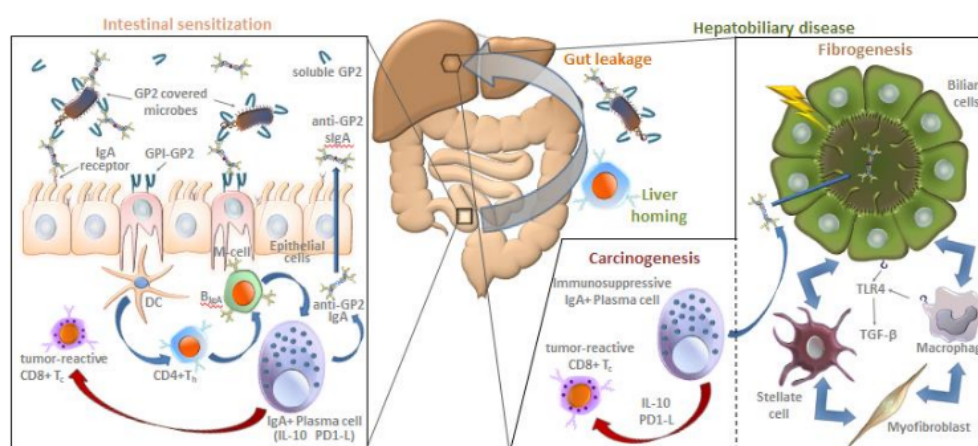
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Figure 1 Autoimmunity-driven putative role of pancreatic glycoprotein 2 in fibro- and tumorigenesis in primary sclerosing cholangitis. Along with digestive enzymes, glycoprotein 2 (GP2) is secreted from pancreatic acinar cells into the intestinal lumen. In addition, GP2 is also expressed on the luminal surface of microfold cells [M-cells in Peyer's patches anchored by glycosylphosphatidylinositol (GPI)]. Both forms of the molecule interact with FimH+ bacteria and opsonize them. The anchored form may be involved in the transcytosis of bound ligands (FimH+ microbes) through M cells, which pass them to antigen-presenting cells like dendritic cells (DC) located in the mucosa-associated immune system. Microbe-bound GP2 epitopes are presented to CD4-positive T helper cells (CD4+ Th) along with bacterial antigens that leads to loss of tolerance to GP2. After clonal expansion, these sensitized cells can "home" to both the gut and the

liver where they trigger (blue arrows) the differentiation of IgA⁺ B cells into IgA⁺ plasma cells. The produced anti-GP2 IgA is actively transported by epithelial cells to the intestinal and biliary lumens as secretory IgA (sIgA) where it binds to GP2. Epithelial cells express IgA receptors on their luminal surface that are involved in active retrograde transport of sIgA molecules (typically coupled by antigens). This process may contribute to bacterial overload of the gut mucosa elevating the levels of bacterial components in the circulation. In the hepato-biliary tract, bacterial components trigger the toll-like receptor 4 (TLR4)-transforming growth factor-β (TGF-β) pathway facilitating fibrosis and cirrhosis. Meanwhile, as a response to the continuous inflammation, a line of IgA+ plasma cells develops an immunosuppressor phenotype expressing interleukin-10 (IL-10) and programmed cell-death 1 Ligand (PD1-L). These molecules inhibit (red arrow) tumor-suppressing cytotoxic CD8⁺ T cells (CD8⁺ Tc) contributing to tumor development in the hepatobiliary and intestinal tract.
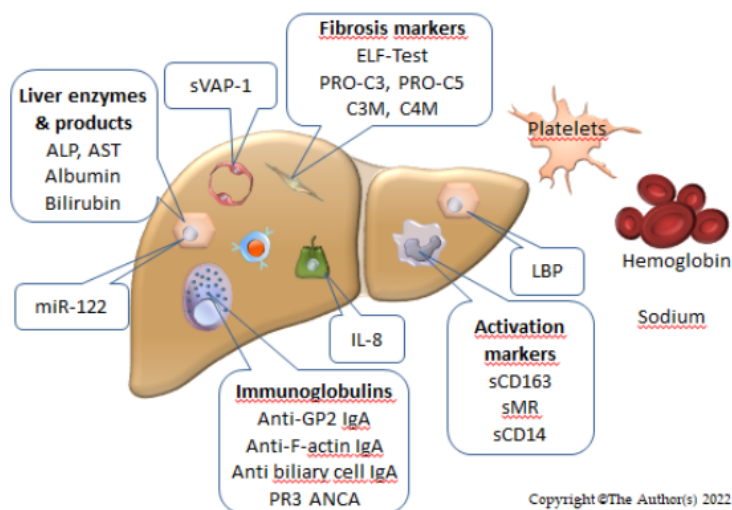

Figure 2 Biomarkers with potential to predict the clinical course of primary sclerosing cholangitis. The markers have various cellular origin, some (LPS-binding protein, interleukin-8, enzymes) have multiple sources that limit their specificity. ALP: alkaline phosphatase; AST: aspartate aminotransferase; GP2: pancreatic glycoprotein 2; IL:

Interleukin; LBP: Lipopolysaccharide binding protein; miR: micro-ribonucleic acid; sMR: Soluble mannose receptor; sVAP: Soluble vascular adhesion protein.

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12   "Diseases of the Liver and Biliary Tree", Springer Science and Business Media LLC, 2021
Crossref
28 words — 1%

13   Emmanuel A Selvaraj, Emma L Culver, Helen Bungay, Adam Bailey, Roger W Chapman, Michael Pavlides. "Evolving role of magnetic resonance techniques in primary sclerosing cholangitis", World Journal of Gastroenterology, 2019
Crossref
27 words — 1%

14   "Poster Sessions", Immunology, 2012.
Crossref
26 words — 1%

15   www.pubfacts.com
Internet
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Internet
23 words — < 1%

17   "Poster Presentations: Posters Friday, 12 April 2019", Journal of Hepatology, 2019
Crossref
22 words — < 1%

18   Aldo J Montano-Loza, Jessica R Allegretti, Angela Cheung, Maryam Ebadi et al. "Single Topic Conference on Autoimmune Liver Disease from the Canadian Association for the Study of the Liver", Canadian Liver Journal, 2021
22 words — < 1%

Crossref

19 Lars Bossen, Mette Vesterhus, Johannes R. Hov, Martti Färkkilä et al. "Circulating Macrophage Activation Markers Predict Transplant-Free Survival in Patients With Primary Sclerosing Cholangitis", Clinical and Translational Gastroenterology, 2021
Crossref
20 words — < 1%

20 Mette Vesterhus, Tom Hemming Karlsen. "Emerging therapies in primary sclerosing cholangitis: pathophysiological basis and clinical opportunities", Journal of Gastroenterology, 2020
Crossref
20 words — < 1%

21 ndl.ethernet.edu.et
Internet
20 words — < 1%

22 www.esp.org
Internet
18 words — < 1%

23 emedicine.medscape.com
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16 words — < 1%

24 Naess, Sigrid, Einar Björnsson, Jarl A. Anmarkrud, Said Al Mamari, Brian D. Juran, Konstantinos N. Lazaridis, Roger Chapman, Annika Bergquist, Espen Melum, Steven G. E. Marsh, Erik Schrumpf, Benedicte A. Lie, Kirsten M. Boberg, Tom H. Karlsen, and Johannes R. Hov. "Small duct primary sclerosing cholangitis without inflammatory bowel disease is genetically different from large duct disease", Liver International, 2014.
Crossref
13 words — < 1%

25 Eirini Bournazou, Jonathan Samuels, Hua Zhou, Svetlana Krasnokutsky et al. "Vascular Adhesion Protein-1 (VAP-1) as Predictor of Radiographic Severity in
12 words — < 1%

Symptomatic Knee Osteoarthritis in the New York University Cohort", International Journal of Molecular Sciences, 2019
Crossref

26 Morten A. Karsdal, Sara T. Hjuler, Yi Luo, Daniel G. K. Rasmussen et al. "Assessment of liver fibrosis progression and regression by a serological collagen turnover profile", American Journal of Physiology-Gastrointestinal and Liver Physiology, 2019
Crossref

12 words — < 1%

27 pubmed.ncbi.nlm.nih.gov
Internet

12 words — < 1%

28 David Bernstein, Alexander J. Kovalic. "Noninvasive assessment of fibrosis among patients with nonalcoholic fatty liver disease [NAFLD]", Metabolism Open, 2022
Crossref

11 words — < 1%

29 pure.rug.nl
Internet

11 words — < 1%

30 M. J. Nielsen, D. Thorburn, D. J. Leeming, J. R. Hov et al. "Serological markers of extracellular matrix remodeling predict transplant-free survival in primary sclerosing cholangitis", Alimentary Pharmacology & Therapeutics, 2018
Crossref

10 words — < 1%

31 Noemi Rotllan, Nathan Price, Paramita Pati, Leigh Goedeke, Carlos Fernández-Hernando. "microRNAs in lipoprotein metabolism and cardiometabolic disorders", Atherosclerosis, 2016
Crossref

10 words — < 1%

32 docplayer.net
Internet

10 words — < 1%

33 Anahita Rabiee, Marina G. Silveira. "Primary sclerosing cholangitis", Translational Gastroenterology and Hepatology, 2021
Crossref

9 words — < 1%

34 Maria Papp, Nora Sipeki, Tamas Tornai, Istvan Altorjay et al. "Rediscovery of the Anti-Pancreatic Antibodies and Evaluation of their Prognostic Value in a Prospective Clinical Cohort of Crohn's Patients: The Importance of Specific Target Antigens [GP2 and CUZD1]", Journal of Crohn's and Colitis, 2015
Crossref

9 words — < 1%

35 hdl.handle.net
Internet

9 words — < 1%

36 journals.lww.com
Internet

9 words — < 1%

37 www.urotoday.com
Internet

9 words — < 1%

38 "Immunoglobulin Secretion in the Airways", Annual Review of Physiology, 03/1990
Crossref

8 words — < 1%

39 Einar Björnsson, Suresh Chari, Marina Silveira, Andrea Gossard, Naoki Takahashi, Thomas Smyrk, Keith Lindor. "Primary Sclerosing Cholangitis Associated with Elevated ImmunoglobulinG4: Clinical Characteristics and Response to Therapy", American Journal of Therapeutics, 2011
Crossref

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