[Frontiers in Bioscience E4, 1683-1705, January 1, 2012]

Primary sclerosing cholangitis: etiopathogenesis and clinical management

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1. ABSTRACT

Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease characterized by the destruction of medium to large-sized bile ducts and intense, concentric fibrosis. Complications from PSC include bacterial cholangitis, cirrhosis, and cholangiocarcinoma and a therapy that might alter the natural history of the disease remains lacking. Our understanding of the pathogenesis of PSC also remains rudimentary but several theories exist, suggesting roles for genetic susceptibility, abnormal innate immune responses lymphocyte trafficking, and toxic bile formation. Medical and surgical therapies, short of liver transplantation, have been disappointing. Currently, the management of PSC is aimed largely at the endoscopic treatment of dominant biliary strictures and complications of cholestasis until the disease has progressed to cirrhosis, at which time liver transplantation is indicated. Progress in our basic understanding of PSC is desperately needed in order to rationally design new therapeutic approaches to this disease.

2. FEATURES OF PSC

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by obliterative fibrosis and inflammation of the intrahepatic and extrahepatic biliary ducts (1-5). It is an insidious but progressive disease, eventually leading to biliary cirrhosis, hepatic failure, and in 10-30% of patients, cholangiocarcinoma (1, 3, 6). Currently, liver transplantation is the only effective treatment available for end-stage liver disease secondary to PSC and as such, PSC is the fifth leading indication for transplantation in the United States (3, 6).

2.1. Epidemiology

PSC is more common in men than woman, and the majority of patients are diagnosed in the third to fourth decade. However, cases are seen in all age groups, and studies in Japan have suggested a bimodal age distribution with a second peak in the seventh decade (7). In addition to

Table 1. Signs and symptoms of PSC at diagnosis.

Symptoms	Prevalence
Asymptomatic	15-44%
Fatigue	43-75%
Pruritus	25-70%
Jaundice	30-69%
Hepatomegaly	34-62%
Abdominal Pain	16-37%
Splenomegaly	14-30%
Hyperpigementation	25%
Weight loss	10-34%
Variceal bleeding	2-14%
Ascites	2-10%

Adapted with permission from references: (53, 214-216)

Table 2. Diseases associated with PSC (25)

Disease	Prevalence
Inflammatory bowel disease	~80%
Type I diabetes mellitus	10%
Thryroid disorders	8%
Psoriasis	4%
Rheumatoid arthritis	3%
Celiac sprue	2%
Systemic lupus erythematosus	2%
Sarcoidosis	1%
Any autoimmune disease	24%
Autoimmune hemolytic anemia	< 1%[1]
Systemic sclerosis/Retroperitoneal fibrosis	< 1%[1]
Immune thrombocytopenia purpura	< 1%[1]

Table 3. Prevalence of abnormal biochemical tests at diagnosis

Test	Patients with abnormal results
Serum alkaline phosphatase	91 – 99%
Serum aminotransferases	95%
Serum bilirubin	41 – 65%
Hypergammaglobulinemia	30%
Serum albumin	20%
Prothrombin time	10%

liver disease, PSC is closely associated with inflammatory bowel disease (IBD). Approximately 75% of patients with PSC have IBD, and of these, nearly 80-90% are diagnosed with ulcerative colitis (UC) (1-3, 8-10). This association with IBD has been noted to be greater in Northern European and American populations than Southern European (50%) and Asian (35%) populations with IBD (7, 11-13).

The true incidence of PSC is unknown, though studies from Oslo, Norway, Sweden, Wales, and Olmstead County, Minnesota estimate it to be between 0.9 and 1.3 cases per 100,000 person-years (6, 14-18). However, a recent study in the UK noted an incidence of 0.41 cases per 100,000 person-years (19). Our own analysis in a population of over three million members enrolled in a large health care system in Northern California found a similar annual incidence of 0.59 cases per 100,000 person-years (unpublished). This discrepancy may be explained by the ethnic diversity of the populations in these latter analyses compared to some of the earlier published studies, particularly as there appears to be a higher prevalence of PSC in Northern Europeans and Caucasians. In contrast, a lower prevalence has been noted in Southern European, Asian, and Alaskan populations, which may be due in part to a lower rate of investigation (11, 12, 20). Regardless, the true incidence of this disease may be underestimated, as it is a relatively rare condition with an insidious course that requires specialized expertise and invasive procedures for diagnosis.

2.2. Clinical features

In the early stages of PSC, most patients are asymptomatic and abnormal liver enzymes may be the only indication of disease. Once advanced, signs and symptoms of cholestasis, portal hypertension and advanced liver disease frequently develop, including fatigue, pruritus, jaundice, weight loss, hepatomegaly, ascites, and abdominal pain (Table 1). With chronic cholestasis, patients are also at risk for developing malabsorption of fat-soluble vitamins, steatorrhea, metabolic bone disease, and cholelithiasis. Bacterial cholangitis may also occur, particularly after endoscopic or surgical procedures. Cholangiocarcinoma, one of the most feared complications of PSC, has an annual incidence of 1.5% per year in PSC patients, with the highest incidence within the first year of diagnosis (14, 21, 22).

As noted, PSC is closely associated with IBD, though the colonic manifestations in these patients are different from patients with IBD alone. This suggests that PSC-IBD is a distinct phenotype. In particular, the colitis of PSC-IBD is often extensive, though clinically quiescent, regardless of whether it is classified as UC or Crohn's disease (CD) (9, 10). Additionally, it is often associated with rectal sparing and backwash ileitis, characteristics typically found in CD (9, 10). In PSC-IBD patients who have undergone proctocolectomy and ileal pouch-anal anastomosis, a higher incidence of pouchitis has been noted (10, 23). Crohn's disease associated with PSC does not typically have strictures or fistulas. Furthermore, some data suggest that PSC-IBD patients are at greater risk for developing colorectal neoplasia, and have lower survival rates than similar IBD patients without PSC (2, 9, 10). Finally, genetic testing has found that of the fifteen susceptible loci for UC, only two are associated with an increased risk of PSC, further supporting that PSC-IBD is a distinct entity (24). In addition to IBD, 24% of PSC patients will also be diagnosed with another autoimmune disease (25), notably type I diabetes (Table 2).

2.3. Biochemical features

As the majority of patients are asymptomatic in the early stages of disease, often PSC is first suspected when biochemical abnormalities are noted on routine or screening laboratories (Table 3). Typically, a cholestatic pattern is appreciated with elevated alkaline phosphatase levels as the predominant feature. Additionally, mild to moderate elevations in serum aminotransferases may be noted though normal liver tests can also be seen. Bilirubin levels are often normal, particularly early in the disease though these can fluctuate at times and often progressively increase as the disease advances (1, 16). Similar to other cholestatic liver diseases, elevated liver and urine copper levels and decreased serum ceruloplasmin may also be present (26). PSC should be considered in all patients with IBD or other autoimmune diseases who are found to have cholestatic liver tests.

2.4. Serologic features

Several autoantibodies have been detected in the serum of PSC patients, though none have been found to have sufficient specificity or sensitivity to be used for screening or diagnosis. The most prevalent autoantibody, perinuclear antineutrophil cytoplasmic autoantibodies, is

Table 4. Prevalence of autoantibodies in patients with PSC.

Autoantibody	Prevalence
Antinuclear antibody	8-77%
Anti-Saccharomyces cerevisiae antibody	20-44%
Antismooth muscle antibody	0-83%
Anticardiolipin antibody	4-66%
Thyroperoxidase antibody	7-16%
Rheumatoid factor antibody	15%
Antimitochondrial antibody	0-9

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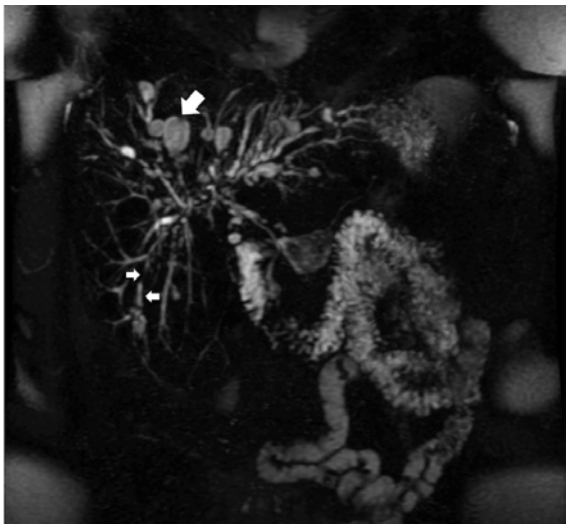

Figure 1. Magnetic resonance cholangiogram of a typical case of primary sclerosing cholangitis, demonstrating strictures and proximal dilation (small arrows) and sacculations (large arrow).

seen in 65-95% of patients with PSC, 50-80% of those with UC, and 10-20% of patients with CD (8, 27-34). Other autoantibodies, such as antinuclear, anti-Saccharomyces cerevisiae, antismooth muscle, anticardiolipin, thyroperoxidase, and rheumatoid factor, are less prevalent (35). Hypergammaglobulinemia and elevated serum IgM levels are also noted in 30% and 50% of patients, respectively (1). IgG4 levels are often elevated in patients with autoimmune pancreatitis, as well as IgG4-related sclerosing cholangitis, which should be distinguished from typical PSC (36, 37). Antimitochondrial antibody is not usually detected in PSC, and can help differentiate PSC from primary biliary cirrhosis (PBC). Table 4 summarizes the prevalence of these autoantibodies in patients with PSC.

2.5. Radiographic features

Cholangiography remains the gold standard for the diagnosis of PSC. Findings of segmental strictures with proximal dilation and sacculation of the bile ducts create the "beaded" appearance that is classic for PSC (Figure 1). Traditionally, cholangiography has been performed through endoscopic retrograde cholangiography (ERC). However, a recent meta-analysis found that magnetic resonance cholangiography (MRC) is sufficiently sensitive and specific to make the diagnosis in many cases of PSC and thus may be a more appropriate first-line diagnostic tool (38, 39). However, if there is a high index of suspicion and MRC is negative or equivocal, ERC should be performed, as MRC has been found to be less sensitive in cases of early disease and cirrhosis (39). Additionally, ERC has the advantage of also being therapeutic, allowing ductal dilation and stenting, and providing further diagnostic information with brush cytology and biopsies. However, it also carries the risk for complications such as pancreatitis, abdominal pain, cholangitis, pancreatitis, bleeding, and bile duct perforation.

2.6. Histologic features

PSC affects both intrahepatic and extrahepatic bile ducts. Biopsies from these ducts show epithelial necrosis and fibrous thickening of the wall, with infiltrate of inflammatory cells. Generally, PSC affects both small and large ducts in the majority of patients though a small subset has involvement of only the small ducts (small duct PSC). Liver biopsy is not reliable alone for the diagnosis of PSC, as it is non-specific and may be normal when only large ducts are involved (40). However, when performed, characteristic findings include bile duct proliferation, periductal fibrosis with typical "onion-skinning" lesions, periductal inflammation, and bile duct obliteration. These histologic features may be classified into four stages using Ludwig criteria: (1) cholangitis or portal hepatitis; (2) periportal fibrosis or hepatitis; (3) septal fibrosis and/or bridging necrosis; (4) biliary cirrhosis (41, 42).

2.7. Diagnostic criteria

Given the heterogeneous nature of PSC and the lack of a quantifiable diagnostic test, strict criteria for establishing the diagnosis of PSC have not been established. Typically, the diagnosis is based upon the presence of a cholestatic pattern of liver biochemistries, typical cholangiographic findings, and the absence of secondary causes of sclerosing cholangitis (43) (Table 5). However, a significant percentage of PSC patients will have normal liver biochemistries, and often the cholangiographic findings are subtle and dependent upon MRC techniques and ERC operator expertise. In addition, PSC patient often have undergone biliary surgery, or may have choledocholithiasis or cholangiocarcinoma (CCA) at the time of diagnosis. Thus, the diagnosis of PSC must be based on a combination of clinical presentation, laboratory and serologic findings, histopathology, and cholangiography.

2.7.1. Small duct PSC

In a small number of patients, PSC involves only the small ducts of the liver without affecting the larger bile ducts. These patients present with typical cholestatic liver tests and liver histology, but normal cholangiograms. The incidence of small duct PSC has not been well-studied, though it is estimated to be as low as 0.15 cases per 100,000 person-years, or approximately 6-16% of the PSC population (16, 44). Most patients with small duct PSC have been noted to have slower clinical progression, with

Table 5. Secondary causes of sclerosing cholangitis.

Cryptosporidium/AIDS cholangiopathy
Cholangiocarcinoma
Choledocholithiasis
Metastatic carcinoma
Eosinophilic cholangitis
IgG4-associated cholangitis
Intra-arterial chemotherapy
Ischemic cholangitis
Mast cell cholangiopathy
Portal hypertensive biliopathy
Recurrent cholangitis
Iatrogenic biliary trauma
Histiocytosis X
Hepatic inflammatory pseudotumor

higher rates of survival and fewer cases of cholangiocarcinoma or transplantation (44, 45). However, approximately 12% of patients with small duct PSC will progress to large duct disease, placing them at similar risks to the general PSC population (44, 45).

2.7.2. PSC-AIH overlap syndrome

PSC-AIH overlap syndrome is the classification given to patients with both the cholangiographic features of PSC and the biochemical and histologic features of autoimmune hepatitis (AIH). More common in children and young adults, the prevalence of PSC-AIH overlap has been reported to be as low as 8% and as high as 49% (46, 47). Such high degree of variability is likely due to the lack of defined diagnostic criteria for this condition. This has led some practitioners, including the International Autoimmune Hepatitis Group, to suggest that these patients should be categorized by their predominant disease, namely PSC or AIH, rather than labeled as an overlap syndrome. However, many clinicians continue to use the term "PSC-AIH overlap syndrome", and define it by such clinical features as high serum aminotransferase levels, normal to high alkaline phosphatase levels, high titers of antinuclear and anti-smooth muscle antibodies, liver pathology with periportal and periseptal lymphocytic piecemeal necrosis, and cholangiographic evidence of PSC (43, 46, 48-50). Furthermore, there has been some evidence to suggest that PSC patients with AIH features may benefit from immunosuppressive therapy, particularly corticosteroids, highlighting the need for further characterization (51).

2.8. Clinical course and prognosis

PSC has a variable clinical course, though the disease most often progresses to end-stage liver disease. The median time from diagnosis to death or liver transplantation ranges from 12 to 18 years (52-54).

Many models have been developed to provide prognostic prediction for life expectancy in PSC patients. The Mayo Clinic Revised Natural History Model for PSC is the most widely accepted model for predicting survival probability (55). This score is based on objective findings of age, bilirubin, albumin, aspartate transaminase, and history of variceal bleeding. However, the accuracy of this model remains poor, and thus cannot be applied to the individual. Recently, Ponsioen et al. have been working to validate the Amsterdam cholangiographic classification system as another prognostic model (54, 56). This system uses qualitative descriptions of the intrahepatic and extrahepatic ductal system, with scores from 0 to 4 depending on the degree of visible abnormality. A combined score has been found to have an inverse relationship to survival and, though subjective, may provide an additional predictive model in the future.

3. ETIOPATHOGENESIS

Despite a number of proposed models to explain the mechanisms involved in PSC, none of them fully explain all the features of PSC, and most lack sufficient supporting evidence. For the most part, these theories attempt to explain the link between IBD and PSC, and several features of this link must be considered. First, the IBD of PSC is a unique entity, often referred to as PSC-IBD (10). Although PSC-IBD has been classically categorized as UC because it usually involves the entire colon, other features including ileal involvement and rectal sparing are more typical of Crohn's disease. It is unclear whether the features of PSC-IBD predispose to PSC or whether they are the result of genetic and environmental factors shared with PSC. Second, PSC is not dependent on active intestinal disease and, in fact, can occur after colectomy (57). Third, immunosuppressive agents, particularly those that are effective for the treatment of IBD, have not been shown to be effective for PSC. Another important feature to be considered is the recurrence of PSC after liver transplantation, suggesting that the target organ has common or generic features that predispose to the immune attack.

Herein, we review the current understanding of the mechanistic hypotheses that have been proposed to explain the pathogenesis of PSC, namely those involving genetic susceptibility, lymphocyte homing, innate immunity and toxic bile. Barriers to the further elucidation of these hypotheses of PSC pathogenesis include: 1) the difficulty in obtaining target tissue, especially in early stages of disease, 2) phenotypic variability and the lack of consensus on classification, 3) the relative rarity of the condition requiring collaboration between multiple institutions, and 4) the absence of an animal model that adequately recapitulates the human condition.

3.1. Genetic susceptibility

Both genetic and non-genetic factors have been identified to predispose to PSC, but how they increase the risk remains largely undefined. Smoking has been repeatedly shown to be a factor that decreases the risk of PSC (58-61). However, this effect may not be directly related to PSC, since smoking also decreases the risk of UC (62). In our recent analysis of patients listed for liver transplantation, PSC was associated with a higher socioeconomic status, independent of age, race, and gender, but urban *versus* rural living had no effect (63). Identification of the specific variables associated with this increased risk may help us to understand the non-genetic susceptibility to PSC.

The importance of genetic susceptibility to PSC is generally accepted, but the strength of the supporting

data is limited. Because PSC is a rare condition, a sufficiently powered concordance study of twins or siblings is not feasible. Nevertheless, in a study of 145 Swedish PSC patients, the prevalence of PSC among their first-degree relatives was approximately 100-times greater than the total population (64). A larger study similarly found that, among a national Swedish cohort of PSC patients (n=678), the risk of cholangitis was increased in offspring, siblings, and parents of the PSC patients, compared to relatives of a control group with hazard ratios of 11.5, 11.1, and 2.3, respectively (65). In an attempt to identify the causative genetic variants for this increased risk, a plethora of candidate gene studies have been reported, ranging from fibrosis mediators to bile acid transporters to immune related genes. In most cases, the studies are underpowered and, with the exception of the Human Leukocyte Antigen (HLA), the results have failed to be replicated in additional cohorts. For example, ICAM-1, which mediates leukocyte adhesion during immune responses and is important in transendothelial migration of neutrophils and T cell activation, has been implicated in UC, as well as a number of other inflammatory disorders including multiple sclerosis and Behcet's disease. Previous studies have demonstrated expression of ICAM on proliferating bile ductules and interlobular bile ducts in PSC patients with advanced disease. The polymorphism K469E in exon 6 leads to a change from glutamic acid to lysine in the immunoglobulin-like domain 5 of ICAM-1, which is thought to affect interactions between LFA-1 and B cells. Although the frequency of the K469E polymorphism was significantly lower in a UK PSC cohort (66), this finding was not replicated in a larger study of Scandinavian PSC cohort (67). Furthermore, most studies have not included an IBD cohort to determine whether associated genes are PSC specific or shared between IBD and PSC. Only recently have the first genome-wide association studies been performed in PSC (68, 69), with the anticipation that additional studies will be performed as soon as adequately large cohorts are collected among international collaborators.

3.1.1. HLA and related gene associations

An association with the HLA complex on chromosome 6p21 with PSC has been well documented from early serologic studies (70, 71). These studies and others have established a strong association in populations of northern European origin between PSC and HLA, 2 susceptibility haplotypes (B*08,DRB1*0301,DQA1*0501,DQB1*0201 and DRB1*13,DQA1*0103,DQB1*0603), and 1 protective haplotype (DRB1*04) (72, 73). More recently, a genome wide association study has established HLA as the most important risk locus by far (68). In this study, a total of 443,816 SNPs were initially genotyped in 285 Norwegian PSC patients and 298 healthy controls, with replication attempted in 3 independent case-control panels from Scandinavia (137 PSC cases and 368 controls), Belgium/The Netherlands (229 PSC cases and 735 controls), and Germany (400 cases and 1832 controls). The strongest associations were detected for HLA-B*08 and DRB*03, with odds ratios of 4.9 and 3.8, respectively. In comparison, the only PSC-specific locus identified to be significant outside the HLA complex, rs9524260 on chromosome 13, showed significant associations in only 3 out of the 4 study panels, with a combined odds ratio of 0.71.

In addition to the strength of this association, the HLA is important for its specificity to PSC relative to UC. HLA is only weakly associated with UC compared to its PSC association (68, 74, 75). In addition, the HLA class II alleles conferring susceptibility to or protection from PSC are found to be associated with PSC patients with or without IBD, and these alleles are not associated with UC (74). Furthermore, the HLA alleles associated with UC are not linked to PSC.

Despite the importance of HLA in PSC, the strong linkage disequilibrium within the HLA region has slowed progress toward identifying the gene or genes that account for the associations. One possible approach to overcome this obstacle is the assessment of HLA associations in the admixed African American population in which the HLA haplotype diversity is much greater (76). In an initial approach, we analyzed HLA allele frequencies in African Americans listed for liver transplantation for PSC or alcoholic liver disease, a condition without any documented HLA associations (63). Importantly, in these African American PSC patients, the B8 and DR13 associations in PSC were replicated, whereas DR3 was not significantly associated with PSC. On the contrary, the negative association with DR4 was detected in African Americans with PSC. Investigation of extended HLA-B and DR haplotypes in African Americans showed that the associated alleles HLA-B8, DR13 or DR4 occurred on several, separate haplotypes, suggesting that HLA-B and HLA-DR associations observed are likely to represent independent phenomena not arising by linkage disequilibrium. These findings illustrate the plausibility of identifying HLA associated susceptibility genes to PSC in African Americans.

Multiple mechanisms supporting the associations with these HLA haplotypes have been put forth, most prominent among them suggesting that these HLA alleles modulate immune responses against specific (auto-)antigens. However, the HLA complex is densely encoded with multiple immunologically important genes that have also been implicated in PSC, specifically major histocompatibility complex class I chain–related A [MICA] and tumor necrosis factor-alpha (TNF-α) (77-80). Associations between HLA-C and HLA-B allele have also been proposed to be related to their interactions with killer immunoglobulin-like receptors (KIRs) on natural killer (NK) cells and various T-lymphocytes (81). NK cell effector function is balanced by inhibitory and activating receptors, such as KIR, which bind HLA class I molecules (82). At least 14 functional KIR genes are present on chromosome 19q13.4, where they exhibit significant allelic and haplotypic variability, the latter of which is largely related to the presence or absence of activating KIR genes. Inhibitory KIRs encode immunoreceptor tyrosine-based inhibitory motifs in their cytoplasmic tails. Activating KIRs interact with DAP12 homodimers that contain

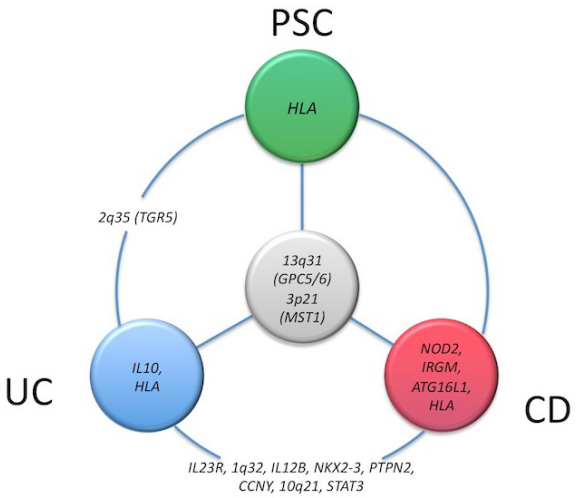

Figure 2. Relationship between genetic loci linked with primary sclerosing cholangitis, ulcerative colitis, and Crohn's disease. Loci at 13q31 and 3p21, which include candidate genes GPC5/6 and MST1, are shared between all three diseases. Several generic IBD loci, including IL23R, 1q32, IL12B, NKX2-3, PTPN2, CCNY, 10q21, and STAT3 are shared by UC and CD but are not associated with PSC. A locus at 2q35 is shared between UC and PSC while no shared loci have been identified between PSC and CD. Although the HLA locus is strongly linked to all 3 diseases, the associated haplotypes are disease specific.

immunoreceptor tyrosine-based activating motifs. Specific combinations of HLA and KIR alleles have been implicated in autoimmunity, tumor immunosurveillance and viral diseases. In a study of Scandinavian PSC patients, the frequency of HLA-Bw4 and -C2, ligands for the inhibitory KIRs 3DL1 and 2DL1, respectively, were significantly reduced compared to controls, suggesting an increase in NK cell activity by decreased inhibition (81). Replication of the decreased HLA-C2 frequency was achieved in an Italian PSC cohort, and was shown to be independent of the HLA class II association (83).

3.1.2. IBD shared loci

With the strong association between PSC and IBD, it would not be surprising if they share some common genetic basis (Figure 2). However, most IBD susceptibility genes tested to date, including those for both UC and CD, have failed to show a common genetic link to PSC (24, 68, 80, 84, 85). The few exceptions to this are loci at *2q35*, *3p21*, and *13q31* corresponding to candidate genes takeda G-protein coupled bile acid receptor 5 (TGR5), macrophage stimulating 1 (MST1), and glypican 5 and 6 (GPC5/6), respectively (68, 75, 86-88). This lack of a more common genetic basis between PSC and UC or Crohn's disease supports the clinical notion that PSC-IBD is a unique phenotype. What role genetic variants in these 3 shared susceptibility loci play in the PSC susceptibility is not clear. At chromosome *2q35*, the bile acid receptor TGR5 gene is one of the most plausible disease genes, as it is strongly expressed in monocytes and macrophages, and inhibits the release of inflammatory cytokines from activated macrophages, including Kupffer cells (89, 90). TGR5 has also been shown to co-localized with and stimulate the activity of the cystic fibrosis transmembrane conductance regulator (CFTR) (91). Interestingly, CFTR has also been implicated in PSC susceptibility (92-95). Recently, sequencing of the *TGR5* gene in 267 PSC patients and 274 controls identified 6 nonsynonymous mutations, 4 of which were found only in PSC patients, and with 3 demonstrating reduced or abolished TGR5 function when incorporated into a reporter construct (96). Fine mapping of the locus around *TGR5*, however, has not been able to definitely localize the region to *TGR5* due to a region of linkage disequilibrium spanning several genes including *IL8RA* and *IL8RB*.

MST1 has been proposed as the most likely candidate gene at the *3p21* locus. MST1 is a circulating protein which exhibits multiple functions including the induction of apoptosis (97), inhibition of LPS-induced cyclooxygenase-2 expression by macrophages via the RON receptor (98), and lymphocyte trafficking by modulating the "inside-out" pathway for lymphocyte function-associated antigen-1 adhesion (99, 100). The PSC-, CD- and UC-associated MST1 variant has been suggested to impair the binding of MST1 to its receptor (101).

3.2. Innate immune response in PSC

The association of PSC with IBD suggests that, like the latter, PSC is not necessarily a classic autoimmune disease in the sense that there is targeted destruction of tissue directed at a specific self-antigen. Rather, IBD is the result of an abnormal innate immune response to antigens of the intestinal flora, which activates an adaptive immune response (102). Genome wide association studies and subsequent functional studies in IBD have implicated several genes such as *NOD2* and *ATG16L1*, both involved in the intracellular processing of bacterial antigens (103-105). In the case of CD this leads to a predominantly T_H-1 type of immune response and increases in IL-17 producing lymphocytes. In contrast, ulcerative colitis tends to be more of a T_H-2 response. Whether PSC, which tends to be characterized by T_H-1cytokines and stricturing reminiscent of CD, involves similar mechanisms has not been fully investigated.

The activation of the innate immune system as a primary inciting event of PSC has been proposed by several investigators (106). According to this theory, PSC is triggered by bacteria or, more likely, pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), lipoteichoic acid, peptidoglycans and unmethylated bacterial dinucleotide motifs that enter the portal circulation through an inflamed, permeable intestine. PAMPs activate macrophages, dendritic cells and NK cells through pattern recognition receptors, including Toll-like receptors (TLRs) and CD14, leading to the secretion of cytokines which, in turn, activate NK cells (IL-12), and promote recruitment and activation of lymphocytes (TNF-α, IL-1βand CXCL8). NK cells may also be activated by MHC Class I chain-related gene products MICA and MICB, which are stress-induced proteins that can promote

the cytotoxic function of NK, NKT and γδT cells through the NKG2D receptor.

Similar to the intestinal mucosa, TLRs are also expressed on the biliary mucosa, and their expression has been shown to be induced in a variety of liver diseases (107). Interestingly, IgG directed against biliary epithelial cells (BEC) has been found in the sera of some PSC patients. These sera induce the expression of TLR4 and TLR9 on BEC in culture, and can be found to co-localize with these same TLRs on BEC *in situ* (108). In fact treatment of BEC with PSC sera-containing anti-BEC antibodies induces secretion of GM-CSF, IL-1β and IL-8, which in turn may lead to the recruitment of neutrophils, macrophages and T cells. However, the target(s) of these anti-BEC antibodies remains unknown.

Macrophages, key cells in the transition from innate to adaptive immune responses, appear to accumulate in the sinusoidal and perisinusoidal spaces in PSC, but not in PBC and other biliary tract diseases. The accumulation is independent of necrosis, cholestasis, and neutrophil infiltration (109). In our previous study of 19 PSC patient liver biopsies, 84% of patients with PSC had inflammatory cells localized to the portal area, although only 4 (21%) were found to have inflammatory cells infiltrating the small bile ducts. When compared to normal subjects, PSC ($P < .0001$) had a significantly higher number of tissue sections with CD68- and/or MPO-positive cells in the portal areas (110).

In animal models, bacterial components can induce a biliary-based inflammation. However, in humans, lipoteichoic acid is relatively infrequent in PSC livers (111). A potential link between bacterial components and hepatobiliary inflammation was first substantiated by Chadwick et al., who demonstrated that N-formylated chemotactic peptides that are produced by several species of intestinal bacteria undergo enterohepatic circulation, and that the levels of these compounds are increased in experimentally-induced colitis (112-114). In addition, rectal administration of N-formyl L-methionine L-leucine L-tyrosine in rats with acetate-induced colitis results in a biliary-based inflammation consisting of macrophages and neutrophils in the early stages, and subsequently CD4+ and CD8+ T cells (115, 116).

In a series of experiments with surgically created self-filling jejunal blind loops leading to bacterial overgrowth, Lichtman et al. demonstrated that, in genetically susceptible rat strains, hepatobiliary injury with features similar to PSC develops, including bile duct proliferation, fibrosis, and acute or chronic periportal and focal parenchymal inflammation (117). The lack of similar findings in self-emptying blind loops that do not develop bacterial overgrowth suggested a role for bacteria, or their cell wall components. The role of bacterial peptidoglycans was supported when the effects of the blind loops were abrogated by oral metronidazole and tetracycline, or by mutanolysin, a muralytic enzyme that cleaves the beta 1-4 N-acetylmuramyl-N-acetylglucosamine linkage of peptidoglycan-polysaccharide (118, 119).

These studies, along with human studies suggesting an increase in intestinal permeability in IBD, make plausible a theory of PSC involving translocation of bacterial cell wall components via the portal circulation to the liver, with further hepatobiliary inflammation and injury, presumably through a pathway that initially involves activation of the innate immune response. However, this model does not have colitis, and there is no evidence that bacterial overgrowth in humans leads to PSC. In fact, Bjornsson et al. concluded that small intestinal bacterial overgrowth and increased intestinal permeability are not important in the pathogenesis of chronic PSC, based on their results that only 1 out of 22 PSC patients had small intestine bacterial overgrowth, and that intestinal permeability of their patients did not differ significantly from that of controls (120).

Organisms postulated to be involved in the induction of the innate immune response in PSC include *Chlamydia spp*. and *Helicobacter pylori*. Ponsioen et al. found an elevated seroprevalence of *Chlamydia*-LPS antibodies in PSC patients compared to a matched control group. The lack of *Chlamydia spp*. in cultures of bile from these patients suggested that these findings were not due to active infection (121). Amplification of 16S ribosomal RNA from explanted livers of 25 patients with PSC detected *Helicobacter* sequences in perihilar ductal and liver tissue of 6 of these patients. However, 3 out of 31 control livers with non-biliary tract disease also demonstrated *Helicobacter* rRNA sequences (122). Similarly, Boomkens et al. reported no significant difference between the incidences of *Helicobacter* DNA in liver tissue from PSC patients compared to controls (123). In addition, there has not been any evidence that *Helicobacter* affects the histology of biliary epithelium (124). Further complicating the interpretation of these studies are the high rates of gram-negative biliary isolates from patients with dominant stenosis, and determining whether these organisms and the immune responses are primary to the disease or secondary to stricturing (125).

Our gene expression profile of PBMC from PSC patients compared to age and sex matched controls using microarray technology also suggests an important role for innate immune response in PSC (126). We identified 942 genes differentially expressed in patients with PSC compared to controls, many of them related to pathways involved in macrophage differentiation by M-CSF, as well as IL-2 receptor β activation of T cells, IL-6 signaling, and MAP kinase-signaling pathways. One of the more interesting genes confirmed to be increased in PSC was TNFAIP6, a 35 kilodalton secreted protein found in many cell types and tissues in response to a variety of stimuli. In particular, TNFAIP6 is expressed in physiologic and pathophysiologic conditions of inflammation, specifically in response to TNF-α and IL-1 (127). Multiple functions have been attributed to TNFAIP6, including inhibition of neutrophil migration, regulation of the protease network, and interactions with multiple glycosaminoglycans. Studies in murine models of arthritis have revealed that TNFAIP6 has potent anti-inflammatory effects through multiple mechanisms. Systemically administered TNFAIP6 induces

Figure 3. Potential mechanisms of innate immunity dysfunction in PSC. MDP is a component of bacterial peptidoglycan common to Gram-positive and Gram-negative bacteria and is a ligand of NOD2. Activation of NOD2 in monocyte-derived DC by MDP induces autophagy and is required for bacterial handling and MHC class II antigen presentation. DC carrying the CD-associated variants in NOD2 and ATG16L1 are defective in these processes. Interestingly, MDP treatment of liver-derived but not splenic-derived plasmacytoid DC (pDC) reduces production of key cytokines including interferon-α, TNF-α, IL-6, and IL-12. In addition, MDP treatment of liver pDC inhibits allostimulatory activation of T cells through the up-regulation of B7-H1, also known as PD-L1. Further, MDP can induce IL1β and IL-18 through the inflammasome receptor NLRP1 which complexes with NOD2 and activates caspase 1.We have observed a high prevalence of CD-associated antibodies to Saccharomyces cerevisiae and the outer membrane porin C (OmpC) of Escherichia coli in PSC patients independent of the presence of IBD suggesting a similar defect in innate and adaptive immune responses (unpublished). In addition, we have seen a higher frequency of IL-18 expressing cells in the sinusoidal portal tracts of PSC livers compared to normal and PBC livers consistent with an increase in caspase 1 activity. Further, tumor necrosis factor-α inducible gene 6 (TNFAIP6), a suppressor of neutrophil function which is produced by DC in response to LPS, is increased in PSC.

greater than 50% inhibition of neutrophil migration in the air pouch model of inflammation. Intravital microscopy suggests that TNFAIP6 influences many aspects of neutrophil extravasation, particularly firm adhesion. In addition, compared to wild-type mice, mice with targeted deletion of *Tnfaip6* show more severe proteoglycan-induced arthritis, which is associated with earlier and more extensive neutrophil infiltration, and elevated levels of serum IL-6. Furthermore, TNFAIP6 induces cyclo-oxygenase-2 expression in macrophages with preferential synthesis of the anti-inflammatory prostaglandin D_2. Notably, these studies do not show any effects of TNFAIP6 on T or B cells responses. Thus, the upregulation of TNFAIP6 in PSC patients may be a marker of intense innate immune responses with TNF-α or IL-1 stimulation, and likely has inhibitory effects on the inflammatory process.

In summary, evidence exists suggesting that the innate immune response plays a role in the pathogenesis of PSC (Figure 3). This may be an insufficient response that fails to clear pathogens leading to chronic, unresolved infection and inflammation. In contrast, the failure to develop tolerance or down-regulate an innate immune response could similarly lead to chronic inflammation.

3.3. Lymphocyte trafficking

The observation that PSC may develop after years after total colectomy, and the lack of correlation between liver disease activity of PSC and intestinal disease activity of IBD, has lead to the hypothesis that the inflammation of PSC is a result of aberrant trafficking of intestinal memory T-lymphocytes to the liver (Figure 4) (128, 129). Supporting this theory is the finding that adhesion molecules and chemokine receptors that are normally restricted to the gut are aberrantly expressed in the liver, presumably leading to the recruitment of intestinal lymphocytes through the enterohepatic circulation (130-135).

Tissue specific recruitment of lymphocytes to inflammation involves the coordinated recognition of "addressins" expressed by vascular endothelial cells by homing receptors on the lymphocyte along with interactions of chemokines and chemokine receptors. In addition to tissue specificity, chemokines and chemokine receptors also impart lymphocyte lineage specificity. For example, T_H1 cells express CCR5 and CXCR3, T_H2 cells express CCR4 and CCR8, T_H17 cells express CCR4, CCR6, and CXCR3, and recently, liver derived regulatory T cells have been characterized as expressing CCR4 and CXCR3 (136). The recruitment of lymphocytes to the liver is unique in many ways, including the dual blood supply entering the liver, the constant exposure of the liver to food and bacterial antigens entering via the portal vein, the low flow state within the hepatic sinusoids, the large fenestrae of the sinusoidal endothelium, and the need for specific recruitment within the liver (*i.e.* portal tract, lobule or biliary epithelium). The roles played by these receptors during recruitment of lymphocytes into the inflamed liver is becoming clearer but, for the most part, does not appear to be disease specific. For a more detailed review of this process, the reader is referred to the excellent review by Oo and Adams (137).

Recruitment of lymphocytes to the intestine involves activation of lymphocytes by dendritic cells in gut associated lymphatic tissue resulting in the expression of

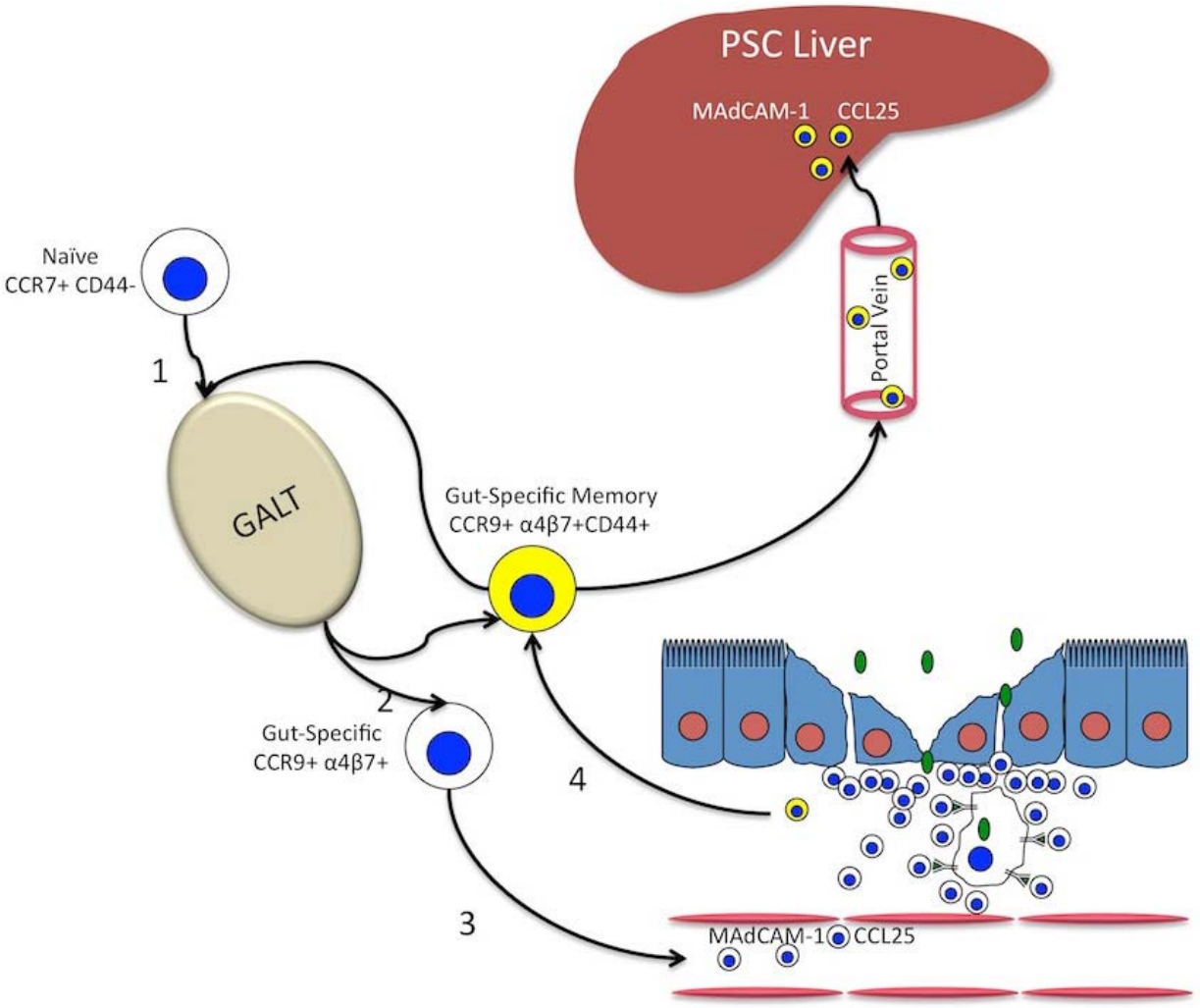

Figure 4. Recruitment of intestinal memory cells to the liver in primary sclerosing cholangitis. (1) Prior to the development of PSC, intestinal lymphocytes are activated in gut associated lymph tissue (GALT) and (2) primed by dendritic cells to express α4β7 and CCR9, which result in (3) the homing of these cells to MAdCAM-1 and CCL25, respectively. (4) Gut-specific memory cells exit into the lymphatics where they may return to the GALT, or possibly circulate to the liver via the portal vein (enterohepatic circulation) or the hepatic artery. Normally the expression of MAdCAM-1 and CCL25 is restricted to the gut, and these cells would continue to circulate. However, in PSC, MADCAM-1 is expressed on portal vein endothelium and CCL25 on periportal sinusoidal endothelium, leading to the recruitment of CD44+ α4β7+ CCR9+ memory cells from the gut. The mechanisms leading to the expression of MAdCAM-1 and CCL25 in the liver are unknown, but the latter appears to be PSC specific. In addition, the recurrence of PSC after liver transplantation suggests that this is not an aberrant property inherent in the PSC liver.

the α4β7 integrin and the CCR9 chemokine receptor. The ligand for α4β7, mucosal addressin cell adhesion molecule-1 (MAdCAM-1), is specifically expressed on the intestinal endothelium and during inflammation on intestinal mucosa. The CCR9 ligand, CCL25, is also capable of activating α4β7, and is expressed preferentially in the intestine as well. The combination of MAdCAM-1 and CCL25 is critical for the specific recruitment of α4β7+CCR9+ lymphocytes to the intestine. MAdCAM-1 was initially thought to be confined to gut endothelium, but has since been shown to be expressed in the portal vein and sinusoidal endothelium in autoimmune mediated liver diseases (138). Grant et al. reported the presence of MAdCAM-1 staining in the portal veins of 11/16 PSC patients, 6/10 AIH patients, and 3/11 PBC patients (134). Dual-color immunofluorescence demonstrated the proximity of α4β7 T-cells to MAdCAM-1 positive vessels, and adhesion assays confirmed the functionality of the interaction. Somewhat surprisingly, however, the frequency of $\alpha_E\beta7+$, but not α4β7+ liver infiltrating lymphocytes (LIL) was increased relative to peripheral blood in PSC. In the only other study of the expression of MAdCAM-1 in human liver diseases, MAdCAM-1 was associated with portal tract inflammation in chronic hepatitis C and B, as well as PBC and PSC (139)

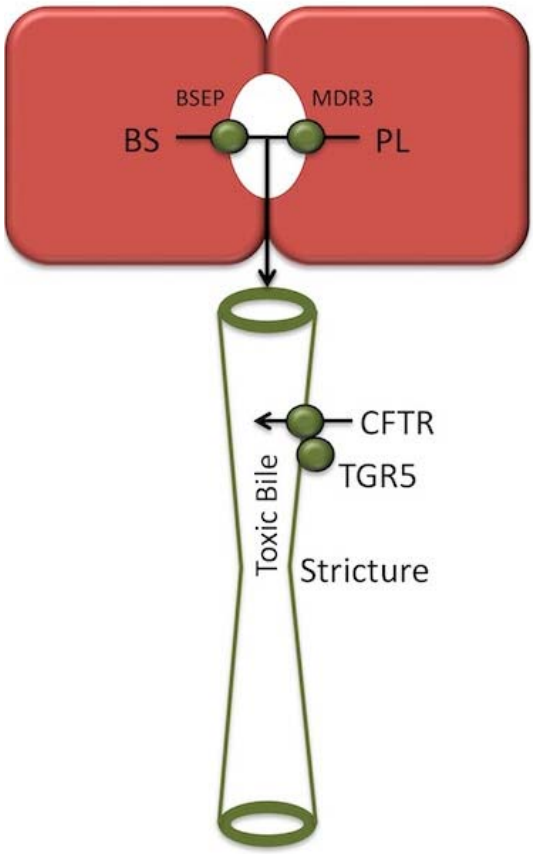

Figure 5. Bile duct injury by toxic bile. Mixed micelle formation protects cholangiocytes from injury in an environment with high concentrations of toxic bile acids. The ratio of bile acid (BA) to phospholipid (PL) is critical for micelle formation and is dependent upon the canalicular transport of bile salts by BSEP and MDR3. Defects in CFTR or its binding partner TGR5 may impair bicarbonate excretion, alkalinization, and hydration of bile. The strictures of PSC may decrease bile flow, and lead to increased exposure of cholangiocytes to bile as well as to increased pressure.

In contrast to α4β7+ LIL, CCR9+ LIL do appear to be specifically increased in PSC compared to PBC. Although the frequency of CCR9+ lymphocytes is not increased in peripheral blood, approximately 20% of LIL from PSC livers express CCR9 compared < 2% in normal livers or PBC (132). This is in comparison to nearly 100% of lamina propria lymphocytes expressing CCR9+ in Crohn's disease. These CCR9+ LIL include CD8+ and CD4+ T cells, the former demonstrating a memory phenotype. The intestinal origin of these α4β7+ CCR9+ lymphocytes is supported by the recent finding that liver dendritic cells and stellate cells were unable to imprint these homing markers on CD8+ T cells (130). The CCR9 ligand CCL25 also appears to be specifically upregulated in PSC liver. Furthermore, CCR9+ LIL preferentially migrate to CCL25 rather than to CXCL12 or CCL5, and are triggered by CCL25 to bind immobilized MAdCAM-1 via α4β7.

Integrin αVβ6 is expressed in large amounts on certain activated epithelia, both mediating attachment to fibronectin and acting as a co-receptor for the activation of latent transforming growth factor (TGF)- β1. In order to elucidate its role in liver fibrosis, Patsenker et al. studied αVβ6 function in rats after bile duct ligation and in *Mdr2*-/- mice. αVβ6 was expressed in large amounts on proliferating bile duct epithelia in fibrosis. In addition, EMD527040, a αVβ6 antagonist, decreased bile ductular proliferation and peribiliary collagen deposition, and down-regulated fibrogenic genes while up-regulating fibrolytic genes. It also reduced endogenous activation of TGF-β1 (140). In human liver, αVβ6 is absent in normal liver, but it is expressed on activated bile duct epithelia and transitional hepatocytes. In chronic hepatitis C, integrin β6 mRNA increases with stage of fibrosis. Thus, αVβ6 does not appear to be a specific receptor targeting lymphocytes in PSC. Clearly a better understanding of the basic biology of lymphocyte homing to the liver and specificity of homing in PSC is needed. In addition, still unknown are the mechanisms leading to the aberrant expression of adhesion molecules and chemokines in the inflamed liver.

3.4. Toxic bile theory

Bile is a complex mixture of bile acids, bilirubin, cholesterol, phospholipids, and proteins, which is toxic to cells even under normal conditions, (141). Several protective mechanisms, including micelle formation and bile flow, prevent injury to biliary epithelial cells despite the high concentration of bile acids normally present. Alterations in the composition of bile, decreased bile flow, and increased biliary pressure may all disrupt the normal bile homeostasis, and lead to toxic bile formation. Bile composition is largely dependent upon excretion of its components across the hepatocyte canalicular membrane, and upon dilution/alkalinization by the cholangiocytes. Bile acids that would induce apoptosis and necrosis of cholangiocytes normally form mixed micelles with phosphotidylcholine and cholesterol to prevent bile acid toxicity. Impairment of transporters responsible for maintaining the bile acid/phospholipid ratio (MDR3 or BSEP) or bicarbonate excretion and hydration of bile (CFTR or AE2) can potentially lead to toxic bile formation. Alternatively, bile stasis, a frequent phenomenon in PSC, may lead to toxic bile formation leading to the exacerbation of bile duct injury (Figure 5).

Support for the toxic bile acid theory comes primarily from the multidrug resistance gene 2 (*Mdr2*) knockout mouse (142-144). Targeted disruption of *Mdr2* leads to sclerosing of the biliary tree with extra- and intrahepatic biliary strictures and dilations, onion-skin type periductal fibrosis, and focal obliteration of bile ducts similar to that seen with primary and secondary sclerosing cholangitis in humans (142). Presumably, biliary phospholipids that are normally transported into bile via the canalicular phospholipids flipase Mdr2 and that form mixed phospholipid-bile acid micelles protect cholangiocytes from bile acid-induced cell injury. Biliary phospholipids are absent in *Mdr2*-/-, which may lead to toxic bile acid-induced damage, resulting in sclerosing cholangitis (145). In addition to toxic bile acids, the

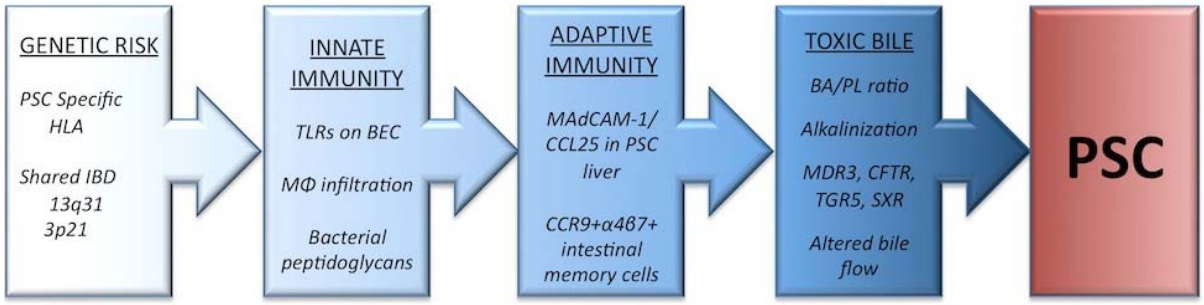

Figure 6. Proposed model of progression to primary sclerosing cholangitis. The model incorporates the many mechanisms that have been proposed for PSC. Genetic factors are important for both the initiation (*e.g.* HLA) as well as the progression of the disease (*e.g.* SXR). Innate immune responses, presumably to bacterial ligands, lead to a chronic inflammatory state and an adaptive immune response, which recruits intestinal memory cells. Alteration in bile composition and bile duct anatomy may be an early event or cause further damage and disease progression.

absence of phospholipids results in cholesterol supersaturated bile, which could facilitate oxidation similar to the process of atherosclerosis (146). Cholangiocytes from *Mdr2*-/- mice express cellular adhesion molecules such as vascular cellular adhesion molecule-1, chemokines, growth factors and cytokines similar to those typical of atherosclerosis, and support some commonality between diseases. However, unlike human PSC, the *Mdr2*-/- mice do not develop IBD (146). In fact, induction of colitis in the *Mdr2*-/- mice had little effect on the sclerosing cholangitis phenotype.

Another potential player in the toxic bile theory is CFTR, the gene responsible for cystic fibrosis. Patients with mutations in *CFTR* are prone to develop a biliary-based cirrhosis, but distinct from PSC. Interestingly, induction of colitis in *Cftr*-/- mice results in bile duct injury (93). Human genetic studies of *CFTR* variants in PSC have been conflicting (92, 94, 95, 147, 148).

Despite the animal models supporting the toxic bile theory, support in humans is generally lacking, particularly as a primary initiating factor. Although some rare variants of *MDR3* have been associated with biliary pathology, including sclerosing cholangitis (149, 150), genetic studies of the human orthologue of *Mdr2* (*MDR3 or ABCB4*) have not found any association of genetic variants with PSC susceptibility (151). In addition, PSC patients with normal serum bilirubin levels have been shown to have normal biliary excretion of bile acids and lipids, suggesting that the toxic bile theory may only play a role in the later stages of PSC (151-153). Further support for the toxic bile theory in disease progression rather than initiation has come from a genetic study linking polymorphisms in the steroid and xenobiotic receptor gene, a ligand-dependent transcription factor that mediates protection against bile acid-induced liver injury in cholestatic animal models, and survival in PSC (154).

The etiopathogenesis of PSC remains enigmatic, and likely involves a series of genetic, environmental, immune, and metabolic events (Figure 6). Genetic susceptibility to the disease is clearly an important factor and, as the specific genetic components are identified, better insights into the mechanisms of this disease will be understood. The paucity of data on the basic characterization of innate immune response in PSC is surprising given its vital role in IBD, particularly Crohn's disease. Although intestinal lymphocytes appear to be recruited from the gut to the liver in PSC, why chronic inflammation and fibrosis occur only in a subset of IBD patients remains to be defined. In addition, an important question remains as to whether this same process holds true for the increasing percentage of PSC patients without IBD. Growing evidence supports a role for the direct action of bile during cholangiocytes damage, but it remains to be established whether this is an early or late event in the disease.

4. CLINICAL MANAGEMENT

As the pathogenesis for PSC remains elusive, targeted medical therapy for this disease has not yet been established. At this time, there are no proven medical therapies for PSC, and the goals of treatment are primarily symptom and complication management. Liver transplantation is the only effective treatment currently available for end-stage PSC at this time.

4.1. Medical Therapy

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid that is the most widely used and studied drug in randomized control trials for PSC. It is a well-established treatment for primary biliary cirrhosis, though its efficacy in PSC appears to be much less certain. Early randomized control trials examined UDCA therapy at low doses (13-15mg/kg/day) and found that there were improvements in biochemical data such as serum bilirubin, alkaline phosphatase, ALT and albumin. However, UDCA did not affect disease progression or development of complications (155). Small cross-sectional and retrospective studies have suggested that patients who receive UDCA may have lower rates for developing colonic neoplasia. However, prospective studies remain to be performed (156, 157). Other studies have also reported improvement in liver histology and cholangiography with UDCA treatment,

though the data for this is limited (158). More recent studies have looked at higher doses of UDCA, but the results have been less than promising. Olsson, et al. performed a randomized study comparing high dose UDCA (17-23mg/kg/day) with placebo in 219 patients with a 5-year follow-up. They did not note any significant benefit in survival or prevention of cholangiocarcinoma, though their study was not sufficiently powered for statistical significance (159). A more recent study by Lindor, et al. randomized 150 patients to even higher doses of UDCA (28-30mg/kg/day) or placebo, and they also noted an improvement in liver tests, but overall, patients taking UDCA had worse clinical outcomes (160). The study was terminated early due to the high rate of the primary outcome in the treatment arm, namely cirrhosis, varices, cholangiocarcinoma, liver transplantation, and death. Thus, given this conflicting data, the American Association for the Study of Liver Disease currently recommends against the use of UDCA therapy in PSC patients while the European Association For the Study of the Liver believes that there is insufficient evidence to make a clear recommendation at this time (43, 161).

As noted above, several theories have been postulated for the development of PSC including autoimmune response, infection, cytokine activation, and bile acid transporter or ion channel abnormality. As such, agents targeting these systems have been investigated in small pilot and animal studies, though they have been largely unsuccessful. In particular, immunosuppressants such as budesonide, cyclosporin, tacrolimus, methotrexate,and mycophenolate mofetil have been studied in randomized trials, though none were found to prolong survival or time to transplantation, and all have serious side effects (1, 43, 162-168). TNF-α inhibitors including pentoxyfylline and etanercept, are another class of immunsuppressants which have been studied, but have not been found to be beneficial (169, 170).

Other agents including antifibrotics such as colchicine and D-Penicillamine have also been proposed, but these have not been clinically efficacious as well (171-173). Nicotine has been studied under the premise that PSC is less common in smokers. However, studies looking at both oral and transdermal administration of nicotine did not show effectiveness (174, 175). Finally, antibiotics have also been suggested with some promising results. A recent pilot study with 16 patients found that minocycline decreased alkaline phosphatase levels and Mayo risk scores though long-term effects were not established (176). In a randomized control trial of 80 patients, those receiving metronidazole combined with UDCA in comparison to UDCA and placebo were found to have lower levels of alkaline phosphatase and Mayo risk score in the study arm, though no significant difference in disease progression (177). Thus, the use of antibiotics for the treatment of PSC remains unclear, though there may be some benefit in chronic use for prevention of bacterial cholangitis (1, 43).

4.2. Management of PSC-Associated Complications

4.2.1. Pruritus

Pruritus is one of the most common symptoms of PSC and can be severely debilitating. For most patients, resin-binding agents such as cholestyramine or colestipol hydrochloride are efficacious as first line therapy (1, 48, 178). However, the etiology of pruritus is not thought to be secondary to retention of bile acids in the skin. Rather, it has been proposed to be a central process, possibly involving increased central opioidergic neurotransmission or activation of serotonergic pathways (179, 180). This may explain why all bile-acid sequestrants are not effective treatments. For example, a recent study examining colesevelam in 35 patients found that, although it decreased bile acid levels, there was no alleviation of pruritus (181). On the other hand, opioid antagonists such as naloxone or naltrexone, and selective serotonin reuptake inhibitors such as sertaline, have been shown to have some benefit (180, 182-184). Rifampin has also been found useful to treat pruritus, though the mechanism for this is unclear (185). Other agents that can also be considered include phenobarbital, anti-histamines, *S*-adenosylmethionine, ondanestron, steroids, and ultraviolet light (1, 179). Refractory cases should prompt investigation for a dominant stricture.

4.2.2. Dominant strictures

Approximately 30–40% of patients develop a dominant stricture defined as a stenosis of ≤ 1.5mm in the common bile duct or ≤ 1mm in the hepatic duct (43). Found to occur in nearly half of patients with PSC, dominant strictures can lead to jaundice and cholangitis (43, 186). Additionally, the presence of strictures raises concern for possible CCA, as this is a common finding in CCA. Of note, a recent study suggested that patients who develop dominant strictures have reduced transplant free survival (187). However, patients who have undergone endoscopic treatment for these stenoses have been found to have predicted survival greater than otherwise (188, 189). Although randomized, controlled trials have not documented a benefit of endoscopic intervention; treatment of dominant strictures is warranted and should be geared towards relieving biliary obstruction and sampling the stricture to evaluate for malignancy. Endoscopic or percutaneous balloon dilation with or without stenting and biliary sphincterotomy are the most common therapies currently performed on dominant strictures. Perioperative antibiotics are often administered as cholangitis can result from instrumentation. Other possible complications include pancreatitis, biliary tract damage or perforation, and hemorrhage (43). For those who fail endoscopic or percutaneous therapy, surgical options are also available, especially for noncirrhotic patients. In particular, hilar and extrahepatic strictures may be resected or a Roux Y hepaticojejunostomy performed (190, 191). This approach should be first line for patients in whom CCA is strongly suspected or previously confirmed.

Bacterial cholangitis frequently occurs in patients who have had a previous biliary surgical procedure and who have an obstructing dominant stricture. Bacterial cholangitis should be treated with broad-spectrum i.v. antibiotics, and drainage in the case of a dominant stricture. For patients with frequent episodes of bacterial cholangitis unresponsive to dilation of dominant strictures, prophylactic or on-demand therapy with ciprofloxacin,

which achieves high biliary concentrations, is often effective.

4.2.3. Cholangiocarcinoma

CCA has been reported to occur in up to 30% of patients. More recent studies report a 10-year cumulative incidence of 7 -9% with the highest incidence within the first year of diagnosis (192-194). Risk factors for CCA include elevated serum bilirubin, variceal bleeding, proctocolectomy, duration of ulcerative colitis, and genetic variants in the NKG2D gene (22, 195). Cholangiocarcinoma carries a poor prognosis, and responds poorly to chemotherapy or radiation therapy. Most liver transplant programs consider cholangiocarcinoma associated with PSC to be an absolute or relative contraindication to liver transplantation (196). However, recent protocols involving stringent pre-transplantation screening and neoadjuvant chemotherapy have reported promising results (197, 198).

Distinguishing a benign stricture from CCA can be difficult. CA19-9 is often elevated in CCA, but it is also elevated in bacterial cholangitis. At a cut-off of 130 U/mL, the sensitivity and specificity are 79% and 98%, respectively (199). Image studies rarely detect CCA, but can be virtually diagnostic with typical features of delayed venous enhancement. Brush cytology has low sensitivity, ranging from 18-40%, but has very high specificity. The presence of polysomy by fluorescent *in situ* hybridization may increase the sensitivity. Positron emission tomography may have a role in the diagnosis of CCA in PSC but further studies are warranted (200-202). There is insufficient evidence to recommend routine screening but annual imaging and CA19-9 is often performed (43).

4.2.4. Metabolic diseases

Hepatic osteodystrophy should be screened for with bone density testing at diagnosis and every 2-3 years. Osteopenia can be treated with calcium (1.0-1.5 g) and vitamin D (1,000 IU), daily. Consideration must be given to administration of bisphosphonates for osteoporosis. Steatorrhea can be caused by a decrease in duodenal concentration of bile acids and thus a decrease in micellar formation, or concurrent conditions such as chronic pancreatitis and celiac disease. Fat-soluble vitamin deficiency (A, D, E, and K) can be related to steatorrhea, but levels of fat-soluble vitamins should be measured even in the absence of steatorrhea and deficiencies treated with replacement therapy.

4.2.5. Gallbladder disease

25% of PSC patients will develop gallstones, usually black pigment stones (203, 204). There is no association with disease stage or use of UDCA. PSC patients are at increased risk of gallbladder carcinoma as well as CCA, and should be screened annually with US(205). Cholecystectomy should be considered in any PSC patient with a gallbladder polyp or mass.

4.3 .Complications of cirrhosis

4.3.1. Peristomal varices

Peristomal varices are common in patients who have undergone a proctocolectomy for underlying inflammatory bowel disease and who have an ileal stoma (206). Bleeding from peristomal varices can be controlled by performing a surgical portosystemic shunt or placement of a transjugular intrahepatic portosystemic shunt. Complications of peristomal variceal bleeding can be prevented by performing an ileoanal anastomotic surgical procedure in patients with PSC who need a proctocolectomy.

4.3.2. Liver Transplantation

Liver transplantation is currently the treatment of choice for patients with end-stage PSC. Liver transplantation in patients with PSC is associated with patient survival rates of up to 90% at 1 year, and 85% at 5 years (43). Indications for liver transplantation are similar to those for other chronic liver diseases. Additional indications include intractable pruritus, recurrent cholangitis, and early cholangiocarcinoma. Recurrence of PSC occurs in up to 20-25% of patients after 5-10 years (207-213). However, the diagnosis of recurrent PSC is difficult because of lack of gold standard diagnostic criteria and potential confounding factors that can mimic PSC including chronic rejection, cytomegalovirus infection, and hepatic artery thrombosis.

5. SUMMARY AND PERSPECTIVE

PSC is an enigmatic inflammatory disease of the liver for which there is an enormous unmet medical need. Progress towards understanding the basis of the disease and new treatment approaches have been slow to emerge. However, with recent multi-institutional collaborative efforts, applications of new technologies, and trials of novel therapies, there is a glimmer of hope for acceleration of PSC discoveries. In the short term, ongoing genetic studies will conclusively identify the genetic variants responsible for known susceptibility loci and discover new PSC specific loci; immunologic studies will reveal the connection between intestinal and liver inflammation; and animal models will aid our understanding of the role of bile acid transport and the biliary epithelial cell in PSC. In the clinical arena, we should expect progress in clinical trials with increased collaboration using non-absorbable antibiotics, farnesoid X receptor agonists, and biologic immunomodulators. Additional needs include the development of a system to meaningfully classify this heterogeneous disease and biomarkers to quantify liver fibrosis and detect early stage cholangiocarcinoma.

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Abbreviations: PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; PBC, primary biliary cirrhosis; ERC, endoscopic retrograde cholangiography; MRC, magnetic resonance cholangiography; AIH, autoimmune hepatitis; HLA, human leukocyte antigen; TNF, tumor necrosis factor; KIR, killer immunoglobulin-like receptor; NK, natural killer; TGR5, takeda G-protein coupled bile acid receptor 5; GPC 5/6, glypican 5/6; CFTR, cystic fibrosis transmembrane conductance regulator; PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharide; TLR, Toll-like receptor; BEC, biliary epithelial cells; MAdCAM-1, mucosal addressin cell adhesion molecule-1; LIL, liver infiltrating lymphocytes; TGF, transforming growth factor; Mdr2, multidrug resistance gene 2; UDCA, ursodeoxycholic acid; CCA, cholangiocarcinoma

Key Words: Primary Sclerosing Cholangitis, Inflammatory Bowel Disease, Genetics, Immunology, Treatment, Review

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