Review

Primary biliary cirrhosis and Sjögren's syndrome: Autoimmune epithelitis

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ABSTRACT

Primary biliary cirrhosis (PBC) has been often coined a model autoimmune disease based on the homogeneity amongst patients, the frequency and similarity of antimitochondrial antibodies, including the highly directed immune response to pyruvate dehydrogenase (PDC-E2). A significant number of patients with PBC suffer from sicca and amongst these, there are patients who also have classic Sjögren's syndrome. Indeed, both PBC and Sjögren's syndrome are characterized by inflammation of target epithelial elements. Both diseases can be considered on the basis of a number of other related clinical aspects, including proposed unique apoptotic features of the target tissue, the role of secretory IgA, and the frequency with which both diseases overlap with each other. Indeed, PBC may be considered a Sjögren's syndrome of the liver, whereas Sjögren's syndrome can be equally discussed as PBC of the salivary glands. Dissection of the genetic predispositions for both diseases and especially the molecular basis of effector mechanisms, will become critical elements in developing new therapies.

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1. Introduction

The current view of autoimmunity is that there will be common susceptibility backgrounds that apply to related pathologies, as supported by the frequent coexistence of more than one autoimmune disease in the same patient, the female predominance [1,2], and the similar genetic associations found within immune-related genes [3,4], along with other common factors [5–7]. One major example of this so-called autoimmune clustering is the coexistence of Sjögren's syndrome (SS) and primary biliary cirrhosis (PBC). These two autoimmune diseases are characterized by the progressive immune-mediated destruction of the epithelial tissues of the salivary and lacrimal glands and the intra-hepatic bile ducts, respectively.

The autoimmune destruction in SS primarily affects exocrine glands and other organs [8] and in 1979 the term "autoimmune exocrinopathy" was coined [9]. More recently, Moutsopoulos suggested the term "autoimmune epithelitis" for the condition to reflect the target of the immune-mediated injury [8]. The rheumatologist or clinical immunologist following patients with SS will often be facing the possibility of encountering some degree of liver damage. This is commonly of secondary clinical relevance to the main diagnosis and the prevalence varies among series and depends on the case-finding criteria.

Earlier studies based on clinical findings and serology estimated that liver abnormalities were found in 18–20% of SS cases to include autoimmune liver diseases and chronic viral hepatitis [10] while liver enlargement was reported during the examination in 2–20% of patients with SS [11–13]. This review will discuss the common themes of PBC that relate to SS and attempt to underline similarities with SS (Table 1) although we admit that numerous peculiarities remain [14–16].

2. Primary biliary cirrhosis (PBC)

PBC is a chronic cholestatic liver disease characterized by the immune-mediated destruction of the epithelial cells lining the small and medium-sized intra-hepatic bile ducts with resulting progressive fibrosis [17]. The diagnosis of PBC is based on the concomitant presence of two out of three internationally accepted criteria [17], i.e. (i) elevation of biochemical indices of cholestasis —e.g. alkaline phosphatase- for more than six months, (ii) the presence of serum antimitochondrial antibody (AMA) at titers exceeding 1:80, and (iii) consistent liver histology (Table 1). In some cases a nuclear magnetic resonance cholangiography is necessary to exclude the involvement of large bile ducts as in primary sclerosing cholangitis. In the past decade, the term "autoimmune

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Table 1
Classification criteria used for PBC and SS.

	PBC [17]	SS [31]
Clinical	Fatigue Pruritus (late stages)	Ocular and oral dry symptoms for longer than 3 months or use of tear substitute more than 3 times a day or recurrent need to drink to swallow dry food
Histology and functional tests	Nonsuppurative cholangitis with interlobular bile duct injury at liver biopsy	Abnormal Schirmer's or Rosa Bengala test or lacrimal gland biopsy with focus score >1 and abnormal sialometry or salivary gland scintigraphy or parotid sialography or salivary gland biopsy with focus score >1
Serum markers	Serum AMA > 1:40 PBC-specific ANA Serum alkaline phosphatase > 1,5-fold the normal value for more than 6 months	Anti-SSA or anti-SSB Rheumatoid factor Speckled ANA

Table 2
Prevalence of serum autoantibodies observed in PBC and SS (highest rates are reported).

	PBC	SS
Antinuclear Ab (ANA)	50% [19]	90% [150]
ANA pattern	Rim-like Multiple nuclear dots	Speckled
Antimitochondrial Ab (AMA)	95% [37]	5% [151]
Anticentromere Ab (ACA)	20% [152]	4% [153]
Anti-SSA/SSB	50% [154]	60% [150,155]
Rheumatoid factor	70% [156]	60% [150]

cholangitis" has been used for patients with PBC but lacking AMA but positive for serum antinuclear (ANA) and anti-smooth muscle (SMA) serum antibody [18,19]. The finding that both the salivary and lacrimal glands [20,21] as well as the urinary tract epithelium could also be injured in PBC led the senior author of this article to suggest that PBC, similar to SS, can be considered a generalized epithelitis [22].

3. Diagnostic criteria

Histology remains crucial when other diagnoses of liver disease have to be ruled out, particularly in AMA-negative patients [23] despite the new diagnostic tools [24–26]. The typical histological lesion for PBC can be summarized as a chronic nonsuppurative destructive cholangitis involving different cell types [27–29] targeting small and medium interlobular bile ducts with a maximum diameter 80 μ. Liver histology and staging manifests a wide sampling variability with four recognized stages ranging from portal inflammation to the appearance of fibrous septa between adjacent portal tracts and ultimately cirrhosis. At advanced stages, PBC cannot be discriminated from cirrhosis of other etiologies [30]. Early disease stages share numerous similarities with SS in which exocrine glands are infiltrated by lymphocytes, mainly CD4$^+$, interfering with the glandular function through the destruction of glandular elements by cell-mediated mechanisms, cytokines that activate pathways characterized by type 1 and 2 interferons, autoantibodies against muscarinic receptors, and metalloproteinases that interfere with the interaction of the epithelium with the extracellular matrix necessary for efficient glandular function [28,31].

Serum autoantibodies remain a crucial tool for diagnostic purposes in rheumatology and this applies to both SS and PBC. Nevertheless, there is limited overlapping in the autoantibody profiles of these two conditions, as illustrated in Table 2, and specific positivities retain their diagnostic power. It is well established that patients with SS commonly have detectable serum anti-Ro/SSA anti-La/SSB and anti-U1RNP [32], while PBC sera are characterized by serum antimitochondrial antibody (AMA), possibly the most specific autoantibody in clinical immunology [33]. AMA are highly specific for PBC and can be detected in nearly 100% of patients when sensitive diagnostic methodologies based on recombinant antigens are used [34,35]. In most clinical settings, however, indirect immunofluorescence techniques are used for

initial screening of cases and might provide falsely positive or negative results. AMA are directed against components of the 2-oxo acid dehydrogenase (2-OADC) family of enzymes within the mitochondrial respiratory chain [36], most frequently the E2 and E3-binding protein (E3BP) components of the pyruvate dehydrogenase complex and the E2 components of the 2-oxo glutarate dehydrogenase and branched-chain 2-oxo acid dehydrogenase complexes. In all three antigens epitopes contain the motif DKA, with lipoic acid covalently bound to the lysine (K) residue. The role of lipoic acid in epitope recognition by AMA is unclear. The pathogenic role of AMA is debatable, since no clinical correlation can be found and animal models developing serum AMA do not develop PBC-like liver lesions.

Serum antinuclear antibodies (ANA) are frequently observed in both conditions but with a higher prevalence in SS compared to PBC. In PBC, these are more frequently of the multiple nuclear dot or rim-like/membranous patterns and possibly more prevalent among AMA-negative PBC patients [19,26,37,38]. The first pattern is produced by autoantibodies against gp210 and nucleoporin 62 within the nucleopore complex and the second pattern by autoantibodies against sp100, promyelocytic leukemia (PML) and small ubiquitin-like modifier (SUMO) proteins [39]. Antibodies against gp210 are associated with a more rapidly progressing disease [40–42], different from serum AMA. AMA are directed at the pyruvate dehydrogenase complex (anti-PDC) and are routinely screened with indirect immunofluorescence. In a multicenter study, AMA were present in 22% of SS, 17% of SLE, 10% of rheumatoid arthritis, and 10% of scleroderma sera [43]. Interestingly, SS *per se* or associated with other autoimmune diseases increases the risk of having positive serum AMA but data are burdened by the lack of more specific recombinant antigens that were recently developed [25,37].

4. Clinical features and management

The major clinical features of PBC and SS are compared in Table 3. PBC at presentation is classically characterized by fatigue and pruritus while physical findings may include skin hyperpigmentation and liver and spleen enlargement [17]. End-stage symptoms are those of all types of liver cirrhosis, including ascites, jaundice, hepatic encephalopathy, and upper digestive bleeding. Fatigue is an incompletely defined, nonspecific symptom that affects up to 70% of patients with PBC and that is often overlooked, particularly in middle-aged women. Importantly, the severity of fatigue is independent of the stage of PBC or its other features (pruritus or severe cholestasis), nor does it depend on psychiatric factors. No medical treatment has been shown to be effective in alleviating this symptom, although fatigue has never been included as an endpoint in any of the large controlled clinical trials [44–49]. As many as 70% of patients with PBC and jaundice suffer from pruritus [50–53]. Longitudinal data show that the vast majority of patients will eventually experience this symptom during their lifetime; pruritus might long precede jaundice onset

Table 3
A comparison of the general features of PBC and SS.

	PBC	SS
Female/male ratio	10:1	9:1
Mean age at diagnosis	55	Bimodal (20, 50)
Disease target	Bile duct, salivary gland epithelia, and uroepithelium	Salivary gland, bile duct, bronchial, alveolar, and tubular epithelia
Environmental factors	Bacteria, xenobiotics	Putative viral infections (EBV, retroviruses)
Epigenetics	Different methylation in hemidesmosome gene; disease-specific miRNAs in minor salivary glands	Different methylation at X-linked promoters
Proteomics	Possible serum biomarkers, no liver tissue disease-specific biomarkers	Proposed salivary biomarkers

and typically worsens at night, following contact with wool, or in warm climates. Despite remaining a challenging symptom, the use of cholestyramine (4 g two or three times a day) ameliorates pruritus while rifampicin has been used to achieve rapid symptom relief; its prolonged use, however, should be avoided. Portal hypertension is frequently found in patients with PBC and, importantly, may precede any other sign or symptom of liver cirrhosis. Over half of untreated patients eventually develop portal hypertension over a 4-year period while medical treatment slows the development of this complication [54,55]; once varices are found, the bleeding prevention or treatment are not different from other chronic liver diseases. An accelerated bone loss is common in long-standing cholestasis compared to sex- and age-matched healthy individuals; this is referred to as metabolic bone disease secondary to reduced bone deposition [56–58]. Current treatment of bone loss includes oral calcium supplementation, weight-bearing activity, and oral vitamin D replacement, if deficiency is found. Postmenopausal hormone replacement therapy should be considered but jaundice and other signs of liver failure should be evaluated during the first months of treatment. Hyperlipidemia is common in up to 85% of patients with PBC and both serum cholesterol and triglyceride high levels can be observed [59–62]; accordingly, statins are usually not necessary but can be well tolerated.

Autoimmune comorbidity is an important feature of PBC. Various disorders, particularly other autoimmune syndromes, are associated with PBC at various degrees [34,63–65]. Our 2005 nation-wide epidemiological study of 1032 patients with PBC reported that one-third of cases are also affected by another autoimmune disease, most commonly SS, Raynaud's phenomenon, autoimmune thyroid disease, scleroderma, and systemic lupus erythematosus, while the prevalence of rheumatoid arthritis did not differ from controls [66]. Interestingly, recent data demonstrated that patients affected by both PBC and scleroderma manifest a less aggressive liver disease, thus suggesting an active interaction between the two conditions [67]; whether this applies also to SS remains to be determined. The association of liver involvement in SS with serum antimitochondrial antibodies (AMA) was first reported in 1970 [68] with studies on well documented SS patient populations, observing a 5–10% antibody prevalence. On one hand, about half of them have elevated liver enzymes while, on the other hand, liver enzymes may be elevated without the coexistence of AMA. According to several studies, characteristic symptoms of SS such as dry mouth or dry eyes are commonly (47–73%) found also in PBC. In addition, objective findings of dry eyes or dry mouth (such as abnormal Schirmer test, or diminished

salivary flow rate) are also found in 30–50% of patients with PBC while radiological findings of sielectasia were demonstrated in 25% of PBC cases. Furthermore, these frequently (26–93%) manifest histological changes compatible with the diagnosis of SS at salivary gland biopsies [12,69,70]. Nevertheless, these individuals differ from the patients with primary SS. They rarely have serious sequelae and their serological and immunogenetic features are not identical to those observed in patients with primary SS. More specific, in these patients anti-Ro autoantibodies are rarely observed and the frequency of HLA-B8, -DR3 and DRW52 is lower compared to patients with primary SS. Thus, SS complicating PBC is considered similar to that occurring in RA patients (secondary SS) [71].

5. Epidemiology and geoepidemiology

In both PBC and SS there is a striking female predominance and female to male ratios as high as 10:1 for PBC and 9:1 for SS [34,72,73]. For both conditions the age at diagnosis is in the mid-50s; however, there are two age peaks of primary Sjögren's syndrome, with the first after menarche during the 20s to 30s and the second after menopause [31,74]. There is a significant variability in the reported prevalence of SS, ranging from 0.2 to 4.8% [75–82], based on the different diagnostic criteria adopted, as illustrated in Fig. 1.

Data about the incidence and prevalence of PBC have generally been obtained through observational (rather than population-based) studies and might not indicate true rates in the general population. While there is general agreement on the simpler diagnostic criteria compared to SS [17], regional differences could vary on the basis of medical awareness and expertise [83]. Indeed, a population-based approach to case detection has little feasibility for PBC because of its rarity and the lack of non invasive tools for most sensitive case-finding. As a result, reported prevalence ranges from 6 to 402 cases per million (Fig. 1) [84–96]. By contrast, findings of serological studies with indirect immunofluorescence in large groups of unselected serum samples show that prevalence of serum AMA in the general population can be as high as 0.5%, with lower frequencies when blood donors are investigated [34]. Different from SS, the variability in the reported estimates of the incidence and prevalence of PBC is likely secondary to different case-finding methods, local physician awareness, and quality levels of health-care systems, as suggested by the socioeconomical differences [66]. On the basis of data from case-finding studies, however, a latitudinal geoepidemiological pattern of occurrence of primary biliary cirrhosis has been proposed, with the disease being more prevalent in northern Europe and North America [97,98].

6. Genetics, epigenetics, and proteomics

Our knowledge of the genetics of SS and PBC remains largely incomplete and is summarized in Table 4. PBC is more frequent in relatives of affected individuals and the term 'familial PBC' has been coined to indicate families that have more than one case. Our data indicate 6% of cases have a first-degree relative that is also affected [66]. More importantly, the concordance rate observed among monozygotic twins for PBC is 63%, amongst the highest reported in autoimmunity, reinforcing the idea of an important role of genetics in disease susceptibility [99]. Due to the rarity of the disease several association studies have attempted to identify genes associated with PBC although no family study of genetic linkage has been performed. Associations are often not applicable to all populations but suggest that a multi-hit genetic model seems to apply to PBC, with different genetic variants conferring susceptibility (first hit) and others influencing disease progression (second hit) [98]. The
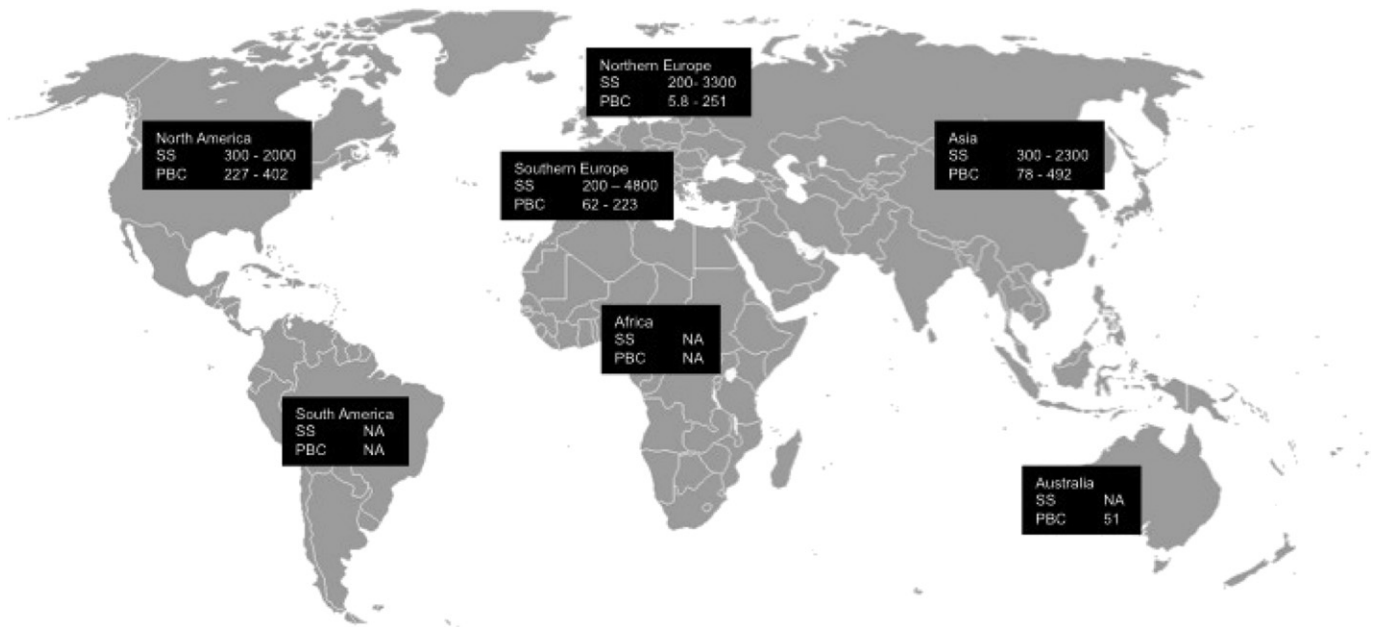
Fig. 1. The worldwide map of PBC and SS geoepidemiology [75—96,159]. Prevalence rate (per million) are illustrated for major areas.

study of the variants of MHC (including type I, II, and III loci) have produced associations that are often weak or limited to specific geographical areas [100]. Following the numerous association studies reported over the past decades for candidate genes in PBC, the first genome-wide case—control association studies were reported in 2009 and 2010 in patients and controls from Canada, the US, and Italy and demonstrated significant associations of PBC with IL12A, IL12RB2, and STAT4 polymorphisms [101,102]. The importance of IL12 was most recently supported by data in a PBC animal model that IL-12p40 is crucial to autoimmunity development thus proving an ideal link between genomic studies and disease pathogenesis with potential therapeutic implications [103]. Furthermore, the growing field of microRNA effects on immune modulation has been investigated also in PBC where a specific signature was described for the first time [104]. Interestingly, this was accompanied also by data obtained in SS [105,106] along with other epigenetic evidence [107,108]. Of note, an age-dependent enhanced monosomy X was reported in peripheral lymphocytes of women with PBC [109] and scleroderma [110], thus suggesting that PBC might ensue from a polygenic model with an X-linked major locus of susceptibility in which genes escaping inactivation are the major candidates [109,111] also based on the presence of AMA in major X chromosome diseases [112].

Beside genetics, our epidemiological data demonstrated that a high risk of developing PBC is associated with a history of urinary or vaginal infections, comorbidity with other autoimmune diseases, lifestyle factors, such as smoking, and previous pregnancies [66]. Experimental studies have focused on two main classes of agents possibly triggering PBC: infectious (bacteria and viruses) and chemical (xenobiotics) [113]. Most evidence has been reported for *Escherichia coli*, while contrasting data have been obtained on the role of *Chlamydia pneumoniae* [114]. Finally, we provided experimental evidence suggesting that *Novosphingobium aromaticivorans*, a ubiquitous xenobiotic-metabolizing Gram-negative bacterium, is the best candidate yet for the induction of PBC [115]. In a complementary fashion, xenobiotics (i.e. foreign compounds that may either alter or complex to defined self or nonself proteins) have been advocated to induce a change in the molecular structure of the native protein sufficient to induce an immune response. Such immune responses may then result in the cross-recognition of the self form, which could in turn perpetuate the immune response, thus leading to chronic autoimmunity. Interestingly, most xenobiotics are metabolized in the liver, thereby increasing the potential for liver-specific alteration of proteins [116].

Epigenetics is an emerging candidate link between genomics and environment in generating phenotype variability and disease susceptibility in adult life [117]. Alterations in the post-translational modification of histones and DNA methylation are the two major epigenetic mechanisms that may potentially cause a breakdown of immune tolerance and the perpetuation of autoimmune diseases as well represented by the most recent data on the hyper-IgM commonly associated with PBC [118]. Several studies both in clinical settings and experimental models proposed that the epigenome may hold the key to a better understanding of autoimmunity initiation and perpetuation. The impact of epigenetic changes has been suggested in systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, in some cases based on observations in animal models. Data on the epigenetics of PBC are limited to one study from our group in which consistent differences were observed in the DNA methylation profile of two X-linked genes (namely CLIC2 and PIN4) in peripheral lymphocytes from discordant twins [119]. This paucity of data is reflected also in SS as only most recently there have been reports of specific microRNAs overexpressed in SS salivary glands [120]. Finally, recent efforts

Table 4
Proposed genetic factors involved in the etiology of PBC and SS. Data are gathered from HLA studies and genome-wide association studies (GWAS) along with the more recent epigenetic data.

	PBC	SS
HLA	DR3, DR8, and DR4 in white, DR2 and DR3 in Japanese, DQA1*0102, and DQ/β1*0402	DR2, DR3
GWAS	DQB1, IL12A, IL12RB2, STAT4, IRF5, IKZF3/ORMDL3, SPIB	STAT4, IRF5
Epigenetics	Different methylation in hemidesmosome gene; disease-specific miRNAs in minor salivary glands	Different methylation at X-linked promoters

have been dedicated to the search through mass spectrometry (MS) for serum biomarkers of autoimmune diseases. This goal is particularly challenging in diseases such as PBC and SS in which liver and minor salivary gland biopsies are still currently used diagnostic tools. MALDI-TOF-MS combined with magnetic beads found in serum of a Chinese cohort of PBC patients found 69 presumable proteins and peptides specifically characterizing PBC [121] but an independent confirmation is awaited. More recently, an MS-based study of PBC and control liver biopsies defined a proteomic profile that characterizes PBC as well as other autoimmune liver diseases [122]. We should note that similar approaches should be encouraged in SS for which biological samples (i.e. saliva) can be easily obtained.

7. Immunopathogenesis

In both PBC and SS serum autoantibodies (AMA and anti-Ro, anti-La for PBC and SS respectively) [32,123−125] target ubiquitous proteins expressed in all nucleated cells [126,127], as illustrated in Fig. 2. Nevertheless, PBC and to a lesser degree SS are organ specific diseases, indicating that epithelia (biliary epithelial cells and salivary gland epithelial cells for PBC and SS respectively) are likely active participants in the pathogenesis of the diseases [128] (Table 5). First, a hypothesis based on the unique apoptosis features in bile duct cells has been proposed to explain PBC tissue specificity [129]. It was first demonstrated that PDC-E2 remains intact and retains its immunogenicity during cholangiocyte apoptosis, secondary to a cell-specific lack of glutathionylation of

biliary epithelial cells [130]. The intact PDC-E2 in apoptotic blebs (i.e. apotopes) could be then uptaken by local antigen presenting cells and transferred to regional lymph nodes for priming of cognate T cells thus initiating PBC [131,132]. Second, biliary epithelial cells are immunologically active because they express HLA antigens, adhesion and costimulatory molecules, such as LFA3, CD40, CD80, CD86, cytokines such as IL6, IL8, chemokines, such as MCP1, and growth factors such as TGF, CTGF, PDGF, endothelin [133,134]. Third, cholangiocytes can secrete secretory IgA in the biliary tree [22,135] with enormous potential implications for PBC pathogenesis as secretory IgA are important effectors in mucosal immunity. IgA derived from local plasma cells are internalized into the epithelial cells as complexes with poly-Ig-receptor, transported to the apical surface of the cell, through a process called transcytosis, and secreted at the mucosal surface after poly-Ig-receptor cleavage. IgA AMA have been detected not only in the bile, but also in the saliva and urine of patients [21,136]. More importantly, it has been demonstrated that IgA AMA are locally produced supporting the hypothesis that other epithelial tissues other than cholangiocytes are involved in PBC. Whether IgA antimitochondrial producing immunocytes are primed in situ or have emigrated from other MALT is unclear but the acquired association between PBC and recurrent urinary tract infections is particularly fascinating [137]. We may hypothesize that bacterial derived mitochondrial antigens in the urinary tract may induce B lymphocyte differentiation into IgA producing plasma cells within uroepithelium. Finally, the salivary gland ducts of patients with PBC, independent of the presence of sicca symptoms, manifests a PBC-like immunohistochemical staining with a monoclonal
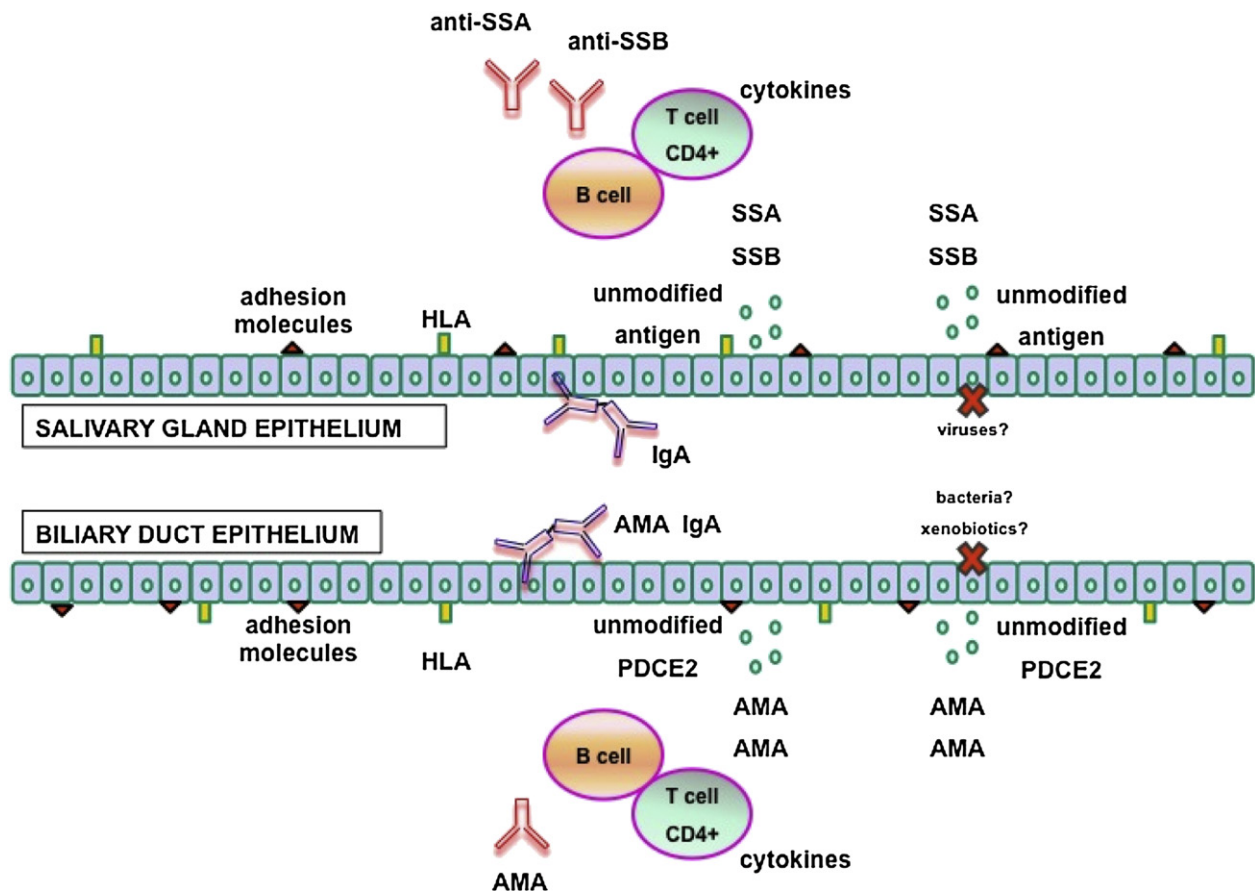

Fig. 2. A parallel comparison of the proposed immunopathogenesis of PBC and SS. In both conditions, environmental triggers (putatively infectious agents and xenobiotics) cause salivary or biliary epithelial cell apoptosis and contribute to tolerance breakdown to self-antigens exposed on the apoptotic blebs (SSA and SSB) and not protected by post-translational modification (PDC-E2). Salivary and biliary epithelial cells concur to the autoimmune process also by expressing cytokines, HLA class II and adhesion molecules.

Table 5
Immunological factors involved in the pathogenesis of PBC and SS.

	PBC	SS
Breaking tolerance trigger	Proposed involvement of infections (E. coli, N aromaticivorans), xenobiotics	Proposed involvement of viral infection (EBV, CMV, retroviruses)
Self-antigen presentation	Lack of gluthationylation of PDC-E2 during apoptosis	Exposure of SSA/SSB on apoptotic blebs and on exosomes; lack of gluthationylation of PDC-E2 during apoptosis
Cellular immune response	Granuloma and predominance of CD4+ infiltrate around bile duct	Predominance of CD4+ infiltrate around salivary duct
Humoral immune response	Epithelial transcytosis of IgA against self-antigen with locally production of AMA in bile, saliva, urine; serum reactivity against PDE2 from cholangiocyte and salivary duct epithelia; disease-specific autoantibodies (AMA)	Epithelial transcytosis of IgA against self-antigen; B cell activation with increased lymphoma risk; not disease-specific autoantibodies (anti-SSA/SSB, rheumatoid factor)

antimitochondrial antibody specific for the self-antigen PDC-E2 [138], further supporting the proposed locally driven autoimmune epithelitis. Finally, we cannot rule out that, similar to what has been reported in multiple sclerosis, post-translational modifications of self-antigens may also play a role in PBC tolerance breakdown [139] as new mechanisms are being proposed for SS [140–142].

8. Treatment

Different from SS in which new treatments are being tested [143–145], the only approved treatment for PBC remains ursodeoxycholic acid (UDCA) at recommended doses of 13–15 mg/kg [23,63]. The mechanism of action of UDCA in PBC is incompletely understood but it has been hypothesized that it is based on different factors, including modification of the bile acid pool, reduction in proinflammatory cytokines, effects on apoptosis and on vasoactive mediators [146]. A meta-analysis demonstrated that an increased survival is only obtained when a dose > 13 mg/kg is prescribed [147,148], despite the fact that a complete biochemical response to UDCA (i.e. normalization of alkaline phosphatase) is achieved in approximately 50% of treated patients. Importantly, none of the medical treatments currently used for SS are contraindicated in patients with coexisting PBC.

Nevertheless, immunosuppressive drugs have also been used in PBC with poor efficacy, including corticosteroids, azathioprine, cyclosporine, methotrexate, penicillamine, and colchicine. Liver transplantation is the ultimate treatment for end-stage PBC but recurrence is common and its rates seem to be influenced by certain immunosuppressive regimens, while the use of UDCA for recurrence is safe and recommended.

Table 6
Proposed animal models for PBC and SS.

PBC [157]	SS [158]
NOD.c3c4	Aec1Aec2
dnTGFβRII	NOD.B10-H2b
IL-2Rα−/−	FS/sld
Ae2(a.b)-deficient	IQI/Jic
Xenobiotic on C57BL/6	CAII immunization
N. aromaticivorans on NOD 1101	PI3 K Knock-out
	ID3 Knock-out
	Ar Knock-out
	Ro immunization
	Aly/aly

9. Conclusions

We speculate that PBC is a classic phenotype of autoimmune epithelitis and this thesis applies to salivary glands and, of course, SS. There are also major differences between SS and PBC and these include the genetic bases of disease susceptibility as well as other mechanisms well illustrated by the available animal models (Table 6). The recently completed genome-wide association studies performed reported a significant association of PBC with polymorphisms of HLA, IL12A, IL12RB2, and to a minor extent, STAT4 [101,102] while data on SS can only be gathered from those in lupus [149] and manifest some degree of similarity with PBC in the minor STAT4 association. Importantly, based on the biology of the target epithelium, there likely are common effector mechanisms. Dissection of these effector mechanisms will become important in any therapeutics. Finally, we submit that PBC and SS comorbidity may identify an intriguing subgroup of patients in which common traits should be investigated.

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