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REVIEW

Sex-related factors in autoimmune liver diseases

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Abstract

Autoimmune diseases are a broad range of diseases in which the immune system produces an inappropriate response to self-antigens. This results in inflammation, damage, or dysfunction of tissues and/or organs. Many autoimmune diseases are more common in women and differences between female and male immune and autoimmune responses have been well documented. In general, most of the autoimmune diseases seem to affect more females, although there are exceptions. Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) are considered to be autoimmune liver diseases (AILD). They all are rare diseases and they result in significant morbidity and mortality. The female predominance in PBC and AIH are among the strongest among autoimmune diseases. However, the mechanisms responsible for the sex differences in autoimmune liver diseases are largely unknown. In this review, we discuss the recent findings on the influence of sex-dependent mechanisms, which may contribute to differences in presentation, clinical characteristics, disease course, and complications observed between female and male patients with autoimmune liver disease.

Keywords Autoimmune hepatitis (AIH) · Primary biliary cholangitis (PBC) · Primary sclerosing · Cholangitis · Pregnancy · Testosterone · Estradiol · X Chromosome · Microbiome

Abbreviations

AIH	Autoimmune hepatitis
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
AILD	Autoimmune liver diseases
LT	Liver transplantation
ANA	Antinuclear antibody
ASMA	Anti-smooth muscle antibody
LKM 1-anti	Liver kidney microsome 1 antibody
anti-LC-1	Anti-liver cytosol type 1 antibodies
AMA	Anti-mitochondrial antibody
PDC-E2	Pyruvate dehydrogenase complex
UDCA	Ursodeoxycholic acid
OVA	Obeticholic acid
IBD	Inflammatory bowel disease
UC	Ulcerative colitis
AP	Alkaline phosphatase
ALT	Alanine aminotransferase
gGT	Gamma-glutamyl transpetidase
HCC	Hepatocellular carcinoma
ER	Estrogen receptor

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Introduction

The leading forms of autoimmune liver diseases (AILD) in both males and females are autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) [52]. All three are complex disorders, which differ according to the site of injury, the pattern of inflammation, and the clinical phenotype [17]. They all follow a progressive course that if untreated develops into liver failure requiring liver transplantation (LT). Strikingly, PBC and AIH are under the greatest female biases among autoimmune

diseases and they occur between three and nine times more frequently in females than in males. Sex may also have an impact on the course of disease and the occurrence of complications, such as hepatocellular carcinoma. The pathophysiology of the sex differences in AILD is unknown; however, factors such as genetic predisposition, sex hormones, and environmental factors alone or—more likely—in combination will contribute. In this review, we discuss recent findings on the influence of sex-specific mechanisms on autoimmune liver disease. First, we will give an overview of the clinical presentation and characteristics of autoimmune liver diseases. We next discuss how sex-related factors, e.g., sex hormones, X and Y chromosomes, microbiome, and environmental factors, may affect autoimmune liver diseases (Fig. 1). Within this review, we thus aim to summarize our understanding of how sex influences the development, progression, and pathogenesis of autoimmune liver diseases.

Autoimmune liver diseases: clinical characteristics and epidemiology

Autoimmune hepatitis

AILD are considered rare diseases; however, there is a marked increase in incidence and prevalence over time. AIH prevalence ranges from 1.68 per 100,000 inhabitants in Europe, yet prevalence and clinical expression vary according to ethnicity [32]. In Denmark, a large population-based study recently assessed the incidence and prevalence of AIH during a nearly 20-year time period. Most strikingly, a marked increase in AIH incidence over time could be observed, which could not be attributed to a relative changes in case ascertainment rates [37]. AIH is characterized by a strong female preponderance (F/M ratio 3–4:1), elevated serum transaminase levels, hypergammaglobulinemia, selectively elevated serum IgG-

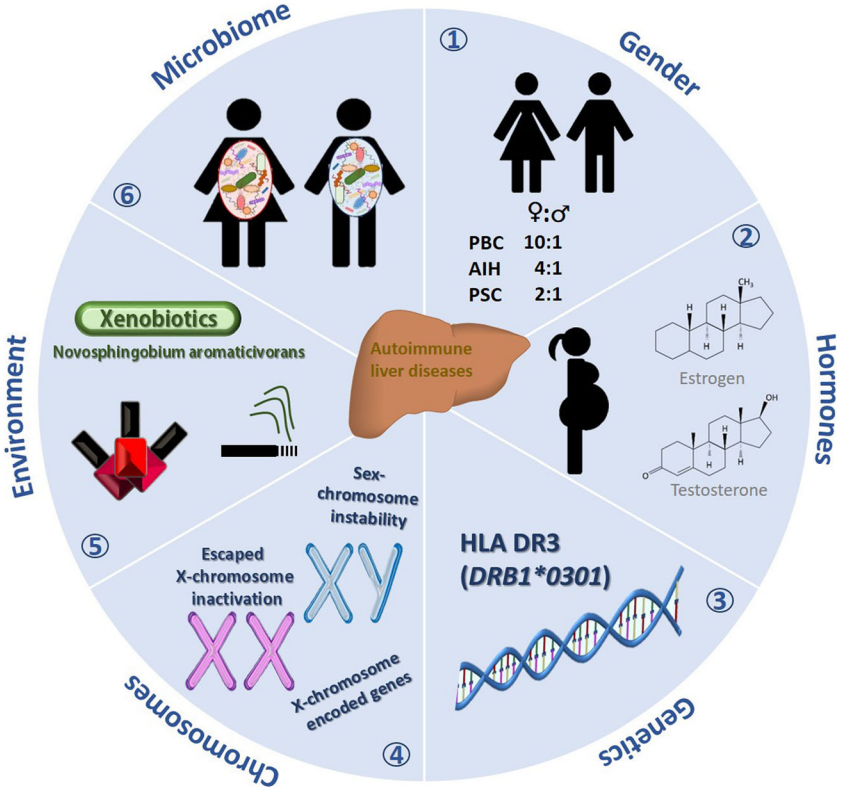

Fig. 1 Overview of sex-related pathophysiological mechanisms in AILD. (1) Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) are among the autoimmune diseases with the greatest female predominance and occur between three and nine times more frequently in females than in males [66, 77]. (2) Observed changes in disease severity during pregnancy and the influence of the sex hormones estrogen and testosterone on immune cells and liver parenchymal cells suggest an influence of sex hormones on intrahepatic inflammation and disease progression [104, 117, 122]. (3) AILD are strongly associated with HLA class I and II-haplotypes. Differences in expression of HLA-DR3 and DR4 alleles in male patients with AIH have been associated with different clinical manifestation and outcome [2]. (4) The involvement of sex chromosomes in the development of AILD has been suggested by findings of decreased DNA methylation of X-chromosome-related genes, sex chromosome instability, and escape from X-chromosome inactivation in patients with PBC [31, 75, 46, 74, 85]. (5) Environmental factors such as xenobiotics, smoking, or beauty products such as nail polish and hair dye were associated with PBC disease progression [86, 99, 109, 118, 130]. (6) The composition of the gut microbiome differs between males and females and may thereby contribute to the observed sex differences in disease susceptibility and disease progression in patients with autoimmune liver disease [38, 114, 116, 102]

levels, presence of autoantibodies, and a liver biopsy typical or compatible with AIH [66, 79]. In most studies, a bimodal age distribution at presentation has been reported with one peak around puberty and another at middle age (fourth to sixth decade of life). In addition, an increasing number of patients diagnosed at ages above 65 have been recently reported [32]. Of note, older patients have been described to be often less symptomatic at presentation and more responsive to treatment [1, 25, 34]. The majority of patients experience slow disease onset and progression with non-specific complaints such as nausea, weight loss, malaise, and fatigue. Approximately half the patients with type 1 autoimmune hepatitis have other autoimmune disorders, such as autoimmune thyroid disease, celiac disease, or rheumatoid arthritis. Acute presentation of AIH is indicated by upper quadrant abdominal pain and arthralgia. However, approximately 25% of patients are diagnosed after incidental discovery of abnormal liver function tests since they are completely asymptomatic with no obvious signs or symptoms of liver diseases [34]. Therefore, AIH presents in advanced stages of fibrosis in around a third of patients [71]. AIH is classified as type 1 or type 2, based on the nature of serum antibodies. Typ-1 as the major type of AIH is characterized by the presence of antinuclear antibodies (ANAs) and/or anti-smooth muscle antibodies (ASMAs). Some patients may present with anti-SLA/LP alone, which is sometimes referred to as type-3 AIH. Anti-liver kidney microsome-1 antibodies (LKM-1) or anti-liver cytosol type-1 antibodies (anti-LC-1) characterize the less common type 2, which is typically seen in children and adolescents [66, 119]. Histologically, AIH is characterized by interface hepatitis, which is dominated by lymphoplasmacytic infiltrates. Approximately 50% of biopsies show some degree of bridging necrosis [119]. An impaired immune reaction of abnormal T lymphocyte to autologous hepatocytes caused by a failure of immunological tolerance is considered to account for the pathogenesis of AIH [41]. However, elevated immunoglobulin levels, autoantibodies, and response to anti-B cell therapy suggest the involvement of B cells in disease pathogenesis [15]. Standard therapy comprises azathioprine and prednisolone and, in the absence of cirrhosis, remission can be achieved in 80% of AIH patients after 6 months of treatment [40, 105].

Primary biliary cholangitis

For PBC, the incidence in European populations is between 1 and 2 per 100,000 population per year with a prevalence reaching 40/100.00 and above [10]. PBC occurs between 40 and 60 years of age [33]. PBC exhibits one of the strongest female preponderances in autoimmune diseases with reported female to male ratio as high as 9:1 although recent data suggest an increasing male prevalence [76, 77]. The most common presenting symptoms in PBC patients are pruritus, fatigue, and Sicca syndrome, whereas 50 to 60% of patients are asymptomatic at diagnosis and identified post screening tests showing elevation of serum alkaline phosphatase or gamma-glutamyl transferase levels. PBC is strongly associated with other autoimmune disorders such as Sjogren's disease and keratoconjunctivitis sicca. PBC is characterized by presence of autoantibodies such as the typical and diagnostic circulating anti-mitochondrial antibodies (AMAs) and PBC-specific ANAs [51, 77]. AMA is the most specific serological marker, detectable in over 90% of PBC patients. In some cases, AMA can be detected before other histological or biochemical signs of liver injury [60]. ANAs can show a PBC-specific pattern that in the case of nuclear rim pattern (gp210) has been shown to identify a subgroup of PBC patients suffering from more advanced/progressive disease [45, 123]. Histological features of PBC include destruction of biliary epithelial cells and loss of small bile ducts (ductopenia) and portal inflammation with granuloma formation [51, 77]. The innate and the adaptive immune system have both been considered involved in multi-lineage loss of tolerance to pyruvate dehydrogenase complex (e.g., PDC-E2) antigens and subsequent development of disease [22, 73, 82, 128]. Standard therapy consists of ursodeoxycholic acid (UDCA) which appears to slow the disease progression in around two thirds of patients, in some improves the quality of life and approach a 10-year survival in 80% for UDCA-treated patients [33, 65]. In contrast, untreated PBC patients presented an average survival of 9–10 years from presentation, with 25% developing liver failure during this time [97]. Besides UDCA, obeticholic acid (OCA), the first in class agonist of farnesoid X receptor (FXR), has recently been approved for second line treatment in patients with insufficient response to UDCA [64, 89]. Based on success rates observed in other autoimmune diseases, use of immunosuppressive drugs has been attempted in PBC. However, classical PBC patients show limited response rates under immunosuppressive treatment [91].

Primary sclerosing cholangitis

The prevalence rate of PSC in Europeans is around 10 per 100,000 population. PSC is diagnosed at all ages, but mean age at diagnosis is approximately 40 years. In contrast to AIH and PBC, PSC is an autoimmune disease with atypical features including an almost equal male to female ratio, the absence of disease-specific autoantibodies, and poor response to immunosuppression [55]. However, some characteristics such as strong HLA- and other genetic associations in immune pathway genes shared by several autoimmune diseases, in addition to histological and serological findings, point to an immune-mediated, if not autoimmune pathogenesis [49, 55]. Although the natural course of PSC may vary from one patient to another, PSC is a chronic liver disease in which periductular inflammation leads to fibrosis of the intra- and/or extrahepatic

bile ducts and multifocal biliary structures [44]. Overall, median transplant-free survival ranges from 12 to 22 years [11, 55]. Patient survival is severely impaired by the high risk to develop hepatobiliary malignancy, especially cholangiocarcinoma [11, 121]. A hallmark of PSC is the strong association with inflammatory bowel disease (IBD), particularly a unique phenotype of ulcerative colitis in around two thirds of cases [44, 78]. Other autoimmune conditions, such as thyroid disease, rheumatoid arthritis, psoriasis, and diabetes mellitus, could be seen in up to 25% of cases. The clinical manifestations are variable and less than 50% of PSC patients are symptomatic at first presentation. The spectrum of symptoms that is reported in a variable number of patients includes pain in the right upper abdominal quadrant, fatigue, pruritus, weight loss, and episodes of fever and chills [20]. The pathogenesis of PSC is unknown, yet a number of mechanisms have been considered in disease development and progression. Among others, defects in mechanisms protecting against bile acid toxicity [28], transport of pro-inflammatory compounds via the portal circulation [54], recruitment of gut-derived T cells to the liver [42], and a dysbalance of TH17 and regulatory T cells [57, 107] have been proposed to contribute to the pathogenesis of PSC. Currently, there is no medical therapy with proven benefit on disease progression [44] and the only treatment effectively improving patient survival is liver transplantation [126]. Of note, PSC recurs in as much as 20–30% of patients within 5 years of liver transplantation [35].

Influence of sex on autoimmune liver diseases

Sex-related effects on clinical presentation and disease course

In addition to affecting prevalence rates, sex may affect the severity of autoimmune diseases, that is, the severity of symptoms, incidence of concurrent diseases, and severity of disease course. In patients with AIH, males presented at a younger age and showed a higher relapse rate compared to female patients [2]. In male patients, an increased expression of HLA-DR3 haplotype has been described. The expression of HLA-DR3 haplotype has been associated with a greater frequency of relapse and younger age of disease onset but does not appear to be associated with a poorer disease outcome [30]. In terms of long-term survival, males appeared to have a better outcome than females [2]. The causes for increased survival in male patients are unknown, but they do not appear to reflect differences in either the time to diagnosis, treatment response, treatment regimen, or frequency of relapses between male and female patients.

Male patients with PBC tend to be less symptomatic at presentation than females, which may result in delayed diagnosis [111]. Females with PBC more often suffer from pruritus than males and it has been suggested that female sex hormones are linked to pruritus development [111]. In addition, fatigue was significantly less marked in male patients with PBC [16]. Concomitant autoimmune diseases such as scleroderma and Sicca syndrome were shown to be less prevalent in men [111]. Men with PBC presented at an older age and seemed to have a more severe disease course and higher overall mortality compared to females with PBC [16]. Levels of alkaline phosphatase (ALP), which is a marker of disease severity, alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (gGT) levels were higher in males than in females and males showed an increased risk for non-response to the standard treatment with UDCA on multivariate analysis [16, 88]. The incidence of hepatocellular carcinoma (HCC) could be significantly greater in men compared to women suffering from PBC [80], which is of major clinical importance. Thus, these data indicate that females are more frequently affected by PBC and are more symptomatic than males, but have a better outcome including better treatment response and less liver-related complications.

Regarding PSC, there is an almost equal sex distribution and no significant differences in age at diagnosis between male and female patients [115]. However, data related to sex differences in disease severity are scarce. A recent publication described that in a retrospective outcome analysis men with classical PSC showed a slight, albeit statistically significant, increased risk of disease progression when compared to women with a matched phenotype [121]. In addition, associated IBD was reported more frequently in males than in females suffering from PSC [115, 121].

Taken together, there is clear evidence for sex affecting incidence, disease manifestation, and course in AIH and PBC, whereas the influence of sex on PSC incidence is much smaller, and its influence on disease course less clear. Clearly, more data is needed on the effects of sex on progression, comorbidity, and mortality in autoimmune liver diseases (Table 1).

Sex hormones and AILD

The outcome of pregnancy in patients with AILD

The evidence for the influence of sex hormones on the development of AILD is mainly based on the observed changes in disease severity during pregnancy. In patients with AIH, previous reports suggested that pregnancy is associated with an increased risk of fetal and maternal complications including fetal loss, pre-term delivery, preeclampsia, and indication for ceasarian section [104]. However, unless pregnancy occurs at advanced disease stages, in most patients a successful pregnancy and delivery of healthy children is possible. Pregnancy may significantly affect the course of disease. Flares in AIH

Table 1 Clinical characteristics and differences compared to female patients in male patients with autoimmune liver diseases primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC)

AIH	♂	Ref
Prevalence compared to female	25%	[32]
Younger age at onset	↑	[2]
Higher relapse rate	↑	[2]
Frequency of HLA-DR3	↑	[30]
Patient survival	↑	[2]
PBC	♂	Ref
Prevalence compared to females	10–20%	[10]
Time to diagnosis	↑	[111]
Puritus, fatigue	↓	[16, 111]
Concomitant autoimmune diseases	↓	[111]
Serum transaminases	↑	[16]
Insufficient UDCA-response	↑	[16, 88]
HCC-incidence	↑	[80]
Patient survival	↓	[80]
PSC	♂	Ref
Prevalence compared to females	50–60%	[115]
Prevalence of associated IBD	↑	[115, 121]
Patient survival	↓	[121]

activity in up to 50% of patients after delivery, occasional flares or AIH manifestations during pregnancy and postpartal development of de novo AIH have been described [14, 39, 48]. In most patients with AIH, the activity of disease significantly declines during pregnancy and treatment intensity can be reduced [14, 124].

Pregnancy in females suffering from primary PBC is uncommon, since most patients diagnosed are above the age of 40 [12]. In a retrospective study of published cases, pregnancy in women with PBC is often symptomatic associated with pruritus but mostly without an increased risk of complications [117]. In the majority of women, the liver biochemistry maintain stable during pregnancy, although an increase of biochemical liver enzymes postnatal is common. Paralleling observations in AIH, a decrease in AMA titers was described, suggesting an immune tolerizing effect of pregnancy also with respect to PBC [95]. However, AMA returned to baseline levels and exacerbations of disease activity were noted in 60% of patients after delivery. These observations might partly be explained by the falling blood concentrations of estrogens after delivery, which facilitates a pro-inflammatory cytokine shift [23].

Regarding PSC, onset of disease usually occurs before the age of 40. However, data on the course of disease and outcome of pregnancy are scarce [50, 122]. Pregnancy did not seem to have a negative impact on short-term disease progression or occurrence of complications, although it occasionally increases itch during the third trimester [122]. Serum liver tests usually remain largely unchanged [122]. The different effects of pregnancy on AILD suggest that the diseases differ in their susceptibility to sex hormone-induced modulation, either by their effects on immune cells or by their immunological or metabolic effects on hepatic parenchymal or antigen-presenting cells.

Immunological effects of sex hormones

Sex hormones (estrogen, testosterone, progesterone, androgens, and prolactin) are apparent candidates for modulating susceptibility to AILDs. A variety of studies suggested that sex hormones could affect both the innate and the adaptive immune systems [23, 72]. In brief oversimplification, estrogens can be summarized as enhancers of humoral immunity and androgens as immune cell suppressors [9].

Estrogen

Estrogens were shown to influence the immune system depending upon the blood level of estrogen, cell type, activation state of cells, and the local environment [59]. Estrogen receptors are expressed in various immune cell types, including macrophages, lymphocytes, and dendritic cells (DC) [61, 113]. Thus, estrogen has been described to enhance the differentiation of immature DC into mature functional DC, which promoted Th1 responses by the expression of cytokines such as IL-6, IL-23, IL-12, and IL-1 beta [29, 108, 110]. However, estrogens were also able to induce a tolerogenic phenotype in DC by decreasing the expression of pro-inflammatory cytokines and by upregulating inhibitory molecules such as PD-L1 and PD-L2 as well as the expression of regulatory cytokines such as IL-10 and TGFbeta [5, 68, 94]. In addition, estrogens have also been shown to modulate the differentiation and function of T cells by promoting IFNgamma production by Th1 cells via potential direct interaction of ER with the IFNgamma promoter [56]. On the other hand, high levels of estrogens skewed the immune response from Th1 to Th2 phenotype [84]. That CD4+ T cells are critical for the progression of PBC has been demonstrated in a murine mouse model of autoimmune cholangitis with female predominance [6]. It has been shown that IFN gamma-induced Th1 responses by CD4 T cell activate and drive sex-biased progression of PBC. In addition, in a recent publication the authors could show that deletion of IFN type I signaling prevents the female-prevalent autoimmune cholangitis phenotype, including portal and lobular bile duct inflammation, granuloma formation, and bile duct damage [7]. So far a direct effect of estrogens on IFNgamma expression has not been shown; however, sex hormones affect expression of some of the pattern of recognition receptors, such as Toll-like receptors, and doing so might indirectly affect the levels of type 1 IFN [18]. Besides affecting immune cells, a direct effect of estrogen on cholangiocytes has

been described. From rat experiments, it has been proposed that estrogen signaling plays a role in the homeostatic proliferative response of cholangiocytes [3]. In a study with postmenopausal PBC patients, immunohistochemical analyses indicate that ER expression was positive in cholangiocytes from early up stage I to stage III while in PBC stage IV, the intralobular bile ducts had lost the positive staining for ER [4]. The expression of ER positively correlated with cell proliferation in patients with early stages while the loss of ER expression in stage IV patients was associated with a loss of proliferation and markedly increased expression of apoptotic TUNEL and Fas markers. Since estrogens have been described to play a major role in promoting the resistance to apoptotic damage and in modulating reparative and inflammatory processes [62], the authors suggests that an estrogen deficiency could favor the evolution of the disease with increased cholangiocyte apoptosis and progression towards the terminal ductopenic stage.

Testosterone

Different studies have examined the suppressive effects of androgens on immune cells. In vitro, naïve T cells, which were re-stimulated with antigen in the presence of testosterone, have been shown to produce higher levels of IL- 5 and IL-10 and decreased levels of IFNgamma, indicating an immune shift of T cells from Th1 to Th2 phenotype [8]. In CD4+ T cells, testosterone can directly act via androgen receptors and induce increased secretion of the anti-inflammatory cytokine IL-10 [70]. Moreover, testosterone has been shown to reduce the production of pro-inflammatory cytokines such as TNF and IL-1beta by human macrophages [27] and monocytes [70]. In human studies, treatment with testosterone had some beneficial effects in male patients suffering from MS [36], a disease with presumed lymphocyte involvement in pathogenesis. In line with this, we could recently describe an important immunosuppressive effect of testosterone on T cell-induced cholangitis. In an antigen-dependent mouse model of experimental cholangitis with a strong female predominance, we identified testosterone as the major sex-specific determinant of liver inflammation: testosterone treatment completely suppressed liver inflammation in female mice and lack of testosterone rendered male mice susceptible to cholangitis development. We could demonstrate that testosterone suppressed the expression of IL-17A by liver infiltrating lymphocytes and the hepatic expression of the lymphotropic chemokines CXCL-9 and CXCL-10 [106]. There is limit data on the role of testosterone for the growth and survival of cholangiocytes. In the bile duct ligation (BDL) model, it has been shown in male rats that androgen receptors (AR) are expressed by cholangiocytes and testosterone-stimulated cholangiocyte proliferation during cholestasis [127]. However, despite the striking sex-related differences in AILD, the influence of sex hormones in terms of intrahepatic inflammation and disease progression remains largely unknown. Functional studies describing the role of sex hormones on immune cell populations and also hepatic parenchymal cells in patients with AILD are lacking and need further investigation.

Sex-related genetic associations in autoimmune liver diseases

PBC, PSC, and AIH all carry a significant association with HLA haplotypes, indicating that the adaptive immune response is involved in disease pathogenesis [53]. In AIH, strongest associations were found within the HLA-DRB1 locus, with alleles encoding for HLA-DR3 and DR4 and the associated alleles, *DRB1*0301* and *DRB1*0401* (66). Male AIH patients showed an increased expression of the HLA-DR3 allele [2] while an increased prevalence of HLA-DR4 in female patients was noted [24]. Both HLA-DR3 (*DRB1*0301*) and DR4 (*DRB1*0401*) have been associated with different clinical manifestations and outcomes. Individuals with HLA DR3 (*DRB1*0301*) develop their disease at an earlier age. They have been described to have a more active disease, as assessed by serum aminotransferase levels and histologic features, than patients with other HLA haplotypes. After corticosteroid withdrawal, relapse rate is more frequently, remission less commonly, and require liver transplantation more frequently. In contrast, patients with HLA DR4 (*DRB1*0401*) are older and more commonly women than patients with HLA DR3 (*DRB1*0301*). HLA DR4 (*DRB1*0401*) patients showed increased serum levels of gamma globulins, greater frequencies of concomitant immunological diseases, and a higher probability of entering remission during therapy [26, 24]. PBC susceptibility is strongly associated with the HLA-DQB1 locus [43] and PSC has been associated with the extended HLA-DRB1*0301-DQA1*0501-DQB1*0201 (DR3) and HLA-DRB1*1301-DQA1*0103-DQB1*0603 (DR6) haplotypes [125]. However, in PBC and PSC, no association between HLA expression and sex or the sex-related influence on disease course has been described so far.

X and Y chromosomes in AILD

Sex chromosomes have been suggested to be partly responsible for the hyper-responsiveness of the female immune system potentially involved in the development of autoimmune liver diseases [67]. Almost all data stem from studies in PBC and there is a considerable lack of information in AIH. The X chromosome encodes many immune-related genes, including CD40 ligand (CD40L), CXCR3, O-linked β-N-acetylglucosamine transferase (OGT), Forkhead Box P3 (Foxp3), Toll-like receptor (TLR) -7, TLR-8, Interleukin-2

Receptor gamma (IL2RG), Bruton tyrosine kinase (BTK), and IL-9R [67]. Epigenetic alterations on the X chromosome, such as decreased DNA methylation of the CXCR3 and CD40L gene promoters, have been reported in female patients with PBC [75]. The level of demethylation of the CXCR3 promoter in CD4+ T lymphocytes correlates inversely with a significantly higher expression of CXCR3 in the same cell subtype of PBC patients. CXCR3 is a pivotal chemokine receptor that coordinates the migration of activated immune cells such as T lymphocytes and NK cells to sites of tissue injury. Increased expression of CXCR3 could therefore promote the progression of PBC [75]. Moreover, it has been recently shown that the X-linked miR-506 gene is upregulated in cholangiocytes which may promote immune activation and PBC disease development by affecting anion exchanger 2 (AE2) and soluble adenylyl cyclase [21, 31], which are responsible to sense the increase in bicarbonate in cholangiocytes and sensitize cells to apoptosis [21].

Sex chromosome instability observed in patients with PBC further supports the involvement of sex chromosomes in the development of PBC. An enhanced X chromosome monosomy rate in peripheral blood cells from female PBC patients [46] and an increased rate of Y chromosome loss in male patients with PBC were observed [74]. Besides epigenetic factors, skewed X-chromosome inactivation (XCI) is considered to be associated with autoimmune diseases in general [13, 92, 93]. Typically, females carry two X chromosomes and to avoid double dosage of proteins paternally and maternally derived X chromosomes were inactivated at almost the same frequency. This results in a 50:50 mix of cells expressing the X chromosome of paternal or maternal origin [96]. However, approximately 15% of X-linked genes escape inactivation [19]. It is suggested that paternal and maternal antigens will be recognized by the immune system within the thymus, and T cells that have a high affinity for such antigens will be deleted by apoptosis [100]. Therefore, XCI in females provides a potential mechanism whereby X-linked self-antigens may escape presentation in the thymus or in other peripheral sites that are involved in tolerance induction [63]. This may lead to the presence of autoreactive T cells and increase the risk of autoimmunity. In several autoimmune diseases associated with PBC, skewed XCI was described, yet XCI did not differ significantly between PBC patients and a control population [47, 85].

Recently it has been described that the X chromosome encoded Toll-like receptor 7 (*TLR7*) escapes X-inactivation in myeloid cells and B cells in females and Klinefelter individuals [112]. Mechanistically, TLR7 activates type I interferon signaling by binding single-stranded RNA. Therefore, a biallelic expression of TLR7 might contribute to a higher risk of developing SLE and other autoimmune disorders in individuals with two X chromosomes. This is of great interest since type I interferon signaling has been described as a key element of sex bias in a murine model of autoimmune cholangitis [7]. One of the genes that controls the expression of IFN1 is IFN regulatory factor 5 (IRF5) and the ectopic expression of IRF5 enabled type I interferon production in response to TLR7 signaling [103]. Of note, IRF5 has been highlighted by genome-wide association study (GWAS) as a risk gene for disease susceptibility in PBC [69].

Sex-dependent environmental factors related to autoimmune liver diseases

Environmental factors are thought to be a triggering event for the development of AID in genetically predisposed individuals of a particular sex and age. Environmental candidates, that have been proposed to play a role in autoimmune diseases, include a broad variety of factors including drugs (medication and/or drug abuse), exposure to chemicals, nutrition, socioeconomic status, microbiome composition, vitamin D deficiency, infectious agents, and both physical and psychological stress [90]. It is tempting to speculate that varying exposure to extrinsic factors such as different dietary habits, increased unprotected exposure to sun in men, and increased use of cosmetic products in women may play a role in sex bias in autoimmune diseases in general. Chemicals commonly found in frequently used beauty products such as nail polish and hair dye were associated with PBC disease progression [99]. Other environmental factors, i.e., Xenobiotics, are foreign compounds that may substitute, alter, or complex to self-proteins and thereby induce a structural change to the native protein structure, which could subsequently break tolerance [120]. In PBC, *Novosphingobium aromaticivorans*, a gram-negative strictly aerobe, has been shown to metabolize xenobiotics capable of altering the host PDC-E2 enzyme, likely through the nucleophilic properties of lipoic acid, finally leading to the loss of tolerance [109]. Smoking in patients with PBC has been associated with advanced histological disease at presentation, but it could be a factor pointing towards increase alcohol consumption as well [130]. However, in PSC patients, smoking has been described to be a protective factor against disease prevalence [86, 118], but the effect of smoking on the progression of PSC has never been studied.

Sex-related differences in intestinal microbiome

Various studies have shown that gut microbiome composition differs between females and males [87, 129], which could potentially contribute to the observed sex-related differences in autoimmune liver diseases. A higher prevalence of type 1 diabetes in females was strongly dependent on the gut microbiota [83, 129]. This finding demonstrated a link between gut

microbes, sex, and autoimmunity. The liver is physiologically exposed to gut-derived microbial components and metabolites because 70% of its blood supply is derived from the portal vein. Intestinal dysbiosis has been described in patients with autoimmune liver disease PBC and PSC [38, 116]. 16sRNA sequencing studies have reported and showed an altered gut microbial community in PSC [58, 101, 102] and PBC patients [81, 114], although there are discrepancies in particular at the genus and species levels. In brief, a microbial signature of 23 genera can be used to precisely distinguish PBC patients from a validation control cohort [114]. Moreover, the gut microbiome in PSC patients shows a marked deviation from healthy controls, characterized by reduced microbial diversity and changes in the abundance of specific bacteria, such as *Enterococcus* and *Veillonella* [98, 101, 102]. Interestingly, *Enterococcus* has been shown to positively correlate with the levels of ALP in univariate analysis, suggesting a potential link between these bacteria and disease severity in PSC [102]. It is therefore tempting to speculate that the intestinal microbiota contributes to the observed sex differences in disease susceptibility and course in patients with autoimmune liver diseases, but further functional studies are clearly warranted.

Concluding remarks

The data reviewed indicate a strong association between the development and disease course of AILD and sex. If we understand sex differences in autoimmune liver disease, we will probably understand a large part of disease pathogenesis in AIH and PBC at least. It is therefore important to improve our functional understanding of sex-specific factors such as sex hormones, sex-related genes, and intestinal microbiota on susceptibility, development, and progression of AILD. Further research on how these factors affect particular populations of immune cells and liver resident cells is required in order to generate novel therapeutic targets for AILD.

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