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REVIEW ARTICLE

The X-factor in primary biliary cirrhosis: monosomy X and xenobiotics

Ilaria Bianchi · Ana Lleo · Francesca Bernuzzi · Lisa Caliari · Dan S. Smyk · Pietro Invernizzi

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Abstract Primary biliary cirrhosis (PBC) is a chronic, cholestatic, autoimmune liver disease characterised by the destruction of small- and medium-sized bile ducts. The serological hallmark of PBC includes antimitochondrial antibodies (AMA). The disease has a striking female predominance, and primarily affects women of middle-age. First-degree relatives, and in particular female relatives, are known to have an increased risk of developing the disease. Several studies have attempted to explain the female predominance of PBC, and autoimmune diseases in general. Two components that are of interest in PBC include monosomy X and xenobiotics. Monosomy X has been noted to be prevalent in the peripheral blood mononuclear cells of PBC patients. Xenobiotics, which are exogenous chemicals not normally found within the body, have been implicated in the modification of, and loss of, tolerance to AMA. Several cosmetics are known to contain these xenobiotics, which is of interest given the information provided in regards to known risk factors for PBC development. This review will focus on X monosomy and xenobiotics, which appear to constitute the X-factor of PBC.

Keywords Autoimmunity · Autoimmune disease · Genetics · Xenobiotics · Monosomy X · Risk factor · Susceptibility

Abbreviations

AMA	Antimitochondrial antibodies
ANA	Antinuclear antibodies
PBC	Primary biliary cirrhosis
PDC-E2	Pyruvate dehydrogenase complex
SSc	Systemic sclerosis
UTI	Urinary tract infection

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease with characteristic immune-mediated destruction of the small- and medium-sized intrahepatic bile ducts, with progression of fibrosis to cirrhosis and liver failure, at which time transplantation is required [1–5]. At the time of diagnosis, patients may be symptomatic or asymptomatic. In asymptomatic cases, patients may have normal or abnormal biochemistry tests, with cholestatic indices being raised [1–3, 6–9]. Symptomatology of PBC generally includes non-specific symptoms such as fatigue, pruritus and arthralgias, with liver disease not being suspected initially [1–3, 6–9]. Advanced symptoms may be related to portal hypertension and hepatic decompensation, including jaundice, ascites or variceal bleeding [1–3, 6–9]. Both symptomatic and asymptomatic patients are usually seropositive for disease-specific autoantibodies such as

I. Bianchi · A. Lleo · F. Bernuzzi · L. Caliari · P. Invernizzi (✉)
Center for Autoimmune Liver Diseases, Humanitas Clinical and Research Center, Via Manzoni 56, 20089 Rozzano (MI), Italy
e-mail: pietro.invernizzi@humanitas.it

D. S. Smyk
Institute of Liver Transplantation, Division of Transplantation Immunology and Mucosal Biology, King's College London School of Medicine at King's College Hospital, London SE5 9RJ, UK

P. Invernizzi
Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis, Davis, USA

anti-mitochondrial (AMA) or disease-specific antinuclear antibody (ANA) [10–14]. The diagnostic criterion of PBC includes: biochemical evidence of cholestasis, the presence of disease-specific AMA and/or ANA, and PBC-specific histopathology [2, 8, 9]. PBC-specific histopathological features include biliary epithelial cell destruction, ductopaenia, portal inflammatory cell infiltration and granuloma formation [2, 3]. Raised alkaline phosphatase and γGT are indicative of cholestasis [1–3, 6–9].

AMA are present in up to 95 % of PBC patients, and are indicative of future development of PBC in asymptomatic patients [1–3, 6–12, 15–17]. This is in contrast to the general population, where the prevalence of AMA is <1 % [18–20]. PBC-specific AMA are directed against components of the 2-oxo-acid dehydrogenase complexes (previously known as M2 antigens), but predominantly recognise the E2 subunit of the pyruvate dehydrogenase complex (PDC) [1–3, 12, 15–17, 21–26]. AMA-positive cases with PBC have antibodies against PDC-E2 in 90 % of cases, and these antibodies also cross-react with the PDC-E3 binding protein (E3BP) [27–29]. Several other targets have been identified, and include the E2 subunits of branched-chain 2-oxoacid dehydrogenase complex (BCOADC) and 2-oxoglutarate dehydrogenase complex (OGDC), and the E1α and E1β subunits of PDC [2, 10, 11, 23, 26–29]. One group in Newcastle has highlighted the significance of AMA, indicating that the majority of asymptomatic, non-cholestatic patients positive for AMA have histological features of PBC [22, 30].

PBC is generally a slowly progressive disease, but the disease course is unpredictable [1–3, 6–9]. The treatment of choice is with ursodeoxycholic acid (UDCA) administered at an appropriate dose (13–15 mg/kg/day) [1–3, 6–9]. UDCA administered in the early phase of the disease can dramatically slow the disease progression, and improve the quality of life in the majority of the patients [1–3, 6–9].

Several risk factors for the development of PBC have been identified in large epidemiological studies (Table 1) [31–35]. Risk factors which have been consistently noted include recurrent urinary tract infections (UTI), cigarette smoking, and estrogen deficiency. Female sex as well as being a first degree relative of a patient with PBC also increases the risk of disease development [31–34, 36]. Genetic and genome-wide association studies (GWAS) have identified several disease susceptibility genes, but it is likely that the development of PBC is multifactorial, with both genetic and environmental factors being involved [37]. Risk reduction, such as hormonal therapy or smoking cessation, and the aggressive treatment of recurrent UTI, has been suggested in PBC patients, based on known risk factors [31–34, 38]. There are currently no reliable prognostic indicators for PBC [2, 6–9].

This review will examine two environmental and genetic factors which appear to play a role in the development of PBC, but may also explain the female predominance of the disease. These factors include xenobiotics, which are extrinsic chemical components found within the body, as well as monosomy X [39].

Genetics and monosomy X

Twin studies have demonstrated that there is a high concordance of PBC among monozygotic twins, and a low concordance among dizygotic twins, which is suggestive of a strong genetic influence [40]. Genetic studies as well as GWAS have identified several genes which appear to be related to PBC [41–49]. In a North American cohort, Hirschfield and colleagues [50] found a strong association between with HLA DQB1, as well as at the IL12A, IL12RB2, STAT4 and CTLA4 loci. That group also identified IRF5-TNPO3, 17q12-21, and MMEL1 loci to also be associated with PBC [51]. A study of Japanese patients found an association with 17q12-21, but no association was found with IL12A, IL12RB2 or IRF5-TNPO3 in that study [47]. Similar findings were reported by Liu and colleagues [52]. Other genes associated with PBC include STAT4, DENND1B, CD80, IL7R, CXCR5, TNFRSF1A, CLEC16A and NFKB1 [53]. More recent data provided strong evidence in support of genetic association of specific HLA and non-HLA genes with PBC [45].

Table 1 Evidence suggesting a role of xenobiotics in the development of primary biliary cirrhosis (PBC)

Evidence	Reference
Hair dyes, nail polish, and smoking are known risk factors	[31–34]
Clusters of PBC near areas of toxic waste	[81]
Induction of AMA in an animal model immunized with 6-bromohexanoate	[86]
Reactivity between several xenobiotics and PBC sera	[88]
AMA-positive PBC sera reacted against 6,8-bis(acetylthio)octanoic acid	[89]
AMA positivity in patients with excessive acetaminophen intake; Immunoreactivity between acetaminophen metabolites and AMA	[90]

Epidemiological studies have indicated that several chemical compounds are risk factors for the development of PBC. Molecular studies have provided evidence to suggest that peptide modification, and mimicry between compounds and AMA, may underlay the loss to tolerance to mitochondrial antigens

As mentioned above, there is a higher risk for PBC development in female relatives of PBC patients, which further suggests that genetic factors are involved in the disease development, and that these factors may be related to the X chromosome [54–65]. As well, genes involved in immunological tolerance are located on the X chromosome, which may also partially explain the predominance of autoimmune disease in females in general [65–68]. Interestingly, a higher frequency of monosomy X in peripheral leukocytes has been found in patients with PBC [39, 66, 67, 69, 70]. One study examined the prevalence of X monosomy via fluorescence in situ hybridisation of peripheral white blood cells in 100 female PBC patients, and 50 patients with chronic hepatitis C and 50 healthy controls [66]. It was found that women with PBC had a higher frequency of monosomy X compared to pathological and healthy controls [66]. That study also noted that the frequency of monosomy X increased with age, which may also contribute to the explanation as to why PBC occurs predominantly in middle-aged women, and is virtually absent in the paediatric age [71–74]. Another study also noted that in addition to PBC, X monosomy was also a feature of systemic sclerosis (SSc) and autoimmune thyroid disease, which are often found to be concomitant in PBC patients [67]. As well, X monosomy was more frequent in peripheral T and B lymphocytes than other blood cell types [67]. Using similar techniques to those above, Svyryd et al. [75] determined the rate of X monosomy in Reynold's syndrome, which is a laminopathy with combined PBC and progressive SSc. X monosomy was found in 12.1 % of Reynold's syndrome, 10 % in PBC, 9.2 % in SSc, and 6.4 % in age-matched healthy controls [75]. Interestingly, an additive effect (89.1 %) of PBC and SSc on the prevalence of X monosomy in Reynold's syndrome patients was noted [75]. As well, the prevalence of X monosomy did not appear dependent on the time of evolution of the autoimmune disease studied [75].

Miozzo et al. [76] set out to determine the mechanism of X chromosome inactivation in 166 female PBC patients and 266 age-matched controls, consisting of both healthy subjects and liver disease patients. That study found that in PBC, X chromosome loss occurred more frequently and in a preferential fashion [76]. That study also highlighted the need to determine the origin of the remaining X chromosome, as imprinting may also play a role in disease development [76]. A recent study by Mitchell et al. [77] tested whether susceptibility to PBC is modified by one or more X-linked gene with variable X chromosome inactivation status, given that 10 % of genes on the X chromosome escape X chromosome inactivation. Peripheral blood mRNA and DNA samples were obtained from monozygotic twin sets both discordant and concordant for PBC [77]. CLIC2 and PIN4 were identified as being consistently down-regulated in the affected twin of discordant pairs [77]. It is likely that more complex epigenetic factors play a role in the development of PBC.

Xenobiotics

Xenobiotics are exogenous chemical compounds that are found within an organism, which are not normally present or expected to be present within that organism. Examples of xenobiotics include antibiotics and pharmaceutical compounds, pollutants, and pesticides to name a few. Xenobiotics have been proposed as a possible environmental trigger of PBC in genetically susceptible individuals [78–83]. Indeed, clusters of PBC have been noted in regions of Newcastle and New York polluted with toxic waste (Table 1) [81]. It is believed that xenobiotics may induce a loss of tolerance by altering or forming complexes with self-peptides, thus eliciting immune response. In PBC, it is possible that a particular chemical compound may alter mitochondrial autoepitopes, or act as mimics to mitochondrial antigens, in a manner similar to molecular mimicry [84, 85]. Leung et al. [86] were capable of inducing AMAs in an animal model when immunised with 6-bromohexanoate conjugated with bovine albumin. Amano et al. [87] demonstrated that continued immunisation of mice with xenobiotics resulted in loss of tolerance to mitochondrial antigens, although this was reversible when exposure to the xenobiotic was stopped. The same group of researchers [88] suggest that the lipoyl domain of the immunodominant E2 component of PDC-E2 is replaced by a chemical xenobiotic mimic, which is capable of breaking self-tolerance in PBC. That group examined 107 potential xenobiotic mimics by coupling them to the lysine residues of the immunodominant region of PDC-E2, and spotted on microarray slides [88]. This was followed by a reactivity assay with sera from 47 PBC patients, 15 with primary sclerosing cholangitis, and 20 healthy volunteers [88]. Thirty-three of 107 xenobiotics had a significant IgG reactivity against PBC sera when compared with control sera, with nine of those compounds being more reactive than the native lipoylated peptide [88]. In addition, absorption studies demonstrated cross-reactivity with lipoic acid in eight of the nine compounds, including 2-octynoic acid, which is used in perfumes, lipsticks and food flavorings [88]. This is of interest given that several epidemiological studies have indicated hair-dye and nail polish use as being a risk factor for the development of PBC [31–34]. A recent study by Naiyanetr et al. [89] showed that AMA-positive PBC sera reacted against 6,8-bis(acetylthio)octanoic acid, which suggests that chemical modification of the lipoyl ring converts lipoic acid to its reduced form which promotes modification by xenobiotics. Therefore, common electrophilic agents such as acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs may induce xenobiotic modification in

genetically susceptible individuals, followed by the production of AMA and possibly PBC [89]. This is of interest given that a recent study has indicated that patients who take an excessive amount of acetaminophen develop AMA with PBC-like specificity, and that metabolites of acetaminophen are immunoreactive with AMA [90]. The above studies demonstrate a possible correlation between risk factors of PBC and the molecular pathways which may be involved in a loss of immunological tolerance. The fact that several of the implicated xenobiotics are components of cosmetics raises the possible link between xenobiotic exposure and female predominance of PBC (Table 1).

Conclusions

Monsomy X and xenobiotics constitute the X-factor of PBC, which takes into account components of genetic susceptibility and environmental triggers, respectively. These components appear to relate to the female predominance of PBC. Further studies are needed to examine the role of epigenetic factors in the induction of PBC. As well, the identification of plausible xenobiotics is needed to allow for testing of these components in PBC patients. An understanding of the genetic components and environmental influences involved in the pathogenesis of PBC, may allow for proper identification of at-risk individuals, as well as possible prevention of the disease development with careful counselling (if possible) in regards to environmental exposure.

Conflict of interest None.

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