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Environmental Factors in Primary Biliary Cirrhosis

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Abstract

The etiology of the autoimmune liver disease primary biliary cirrhosis (PBC) remains largely unresolved, owing in large part to the complexity of interaction between environmental and genetic contributors underlying disease development. Observations of disease clustering, differences in geographical prevalence, and seasonality of diagnosis rates suggest the environmental component to PBC is strong, and epidemiological studies have consistently found cigarette smoking and history of urinary tract infection to be associated with PBC. Current evidence implicates molecular mimicry as a primary mechanism driving loss of tolerance and subsequent autoimmunity in PBC, yet other environmentally influenced disease processes are likely to be involved in pathogenesis. In this review, the authors provide an overview of current findings and touch on potential mechanisms behind the environmental component of PBC.

Keywords

autoimmunity; environment; primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by chronic inflammation and targeted destruction of biliary epithelial cells lining the small- to medium-sized interlobular bile ducts.¹ As with most other autoimmune diseases, development of PBC is thought to entail the action of environmental stressors in genetically susceptible individuals.² However, the etiology of this disease remains enigmatic despite much recent effort, reflecting the true complexity underlying autoimmunity and the difficulties inherent to understanding and testing how environmental factors interact with the genetic background to result in disease.

Robust genetic associations with specific human leukocyte antigen (HLA) alleles, a marked female predominance, and the near ubiquity of antimitochondrial antibodies (AMAs) specific for the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) in PBC patients indicate that PBC is a prototypical autoimmune disease.³ Evidence for the role of genetic factors is provided by high disease concordance in monozygotic (MZ) twins,⁴ increased sibling risk of AMA positivity⁵ and PBC development,⁶ and overlap with other autoimmunity.⁷ Additionally, recent genome-wide association studies (GWASs) and follow-

up fine mapping efforts^{8–14} have identified some 30 independent association signals primarily implicating genes with known immunological function and involving IL12, Jak-Stat, and NF- κ B signaling pathways. As a rule, these associations have demonstrated relatively low penetrance and many of the PBC-associated loci overlap with signals obtained for other autoimmune diseases, suggesting that common genetically encoded differences in immune function contribute to the spectrum of autoimmunity. However, the factors responsible for the development of organ-specific disease such as in PBC remain elusive.

Although genetic factors play an important role in the development of complex autoimmune disease, it is becoming apparent that environmental exposures are equally important. Environmental factors likely affecting PBC include chemical toxins, xenobiotics, and infectious agents that ultimately drive loss of tolerance to mitochondrial antigens through a variety of mechanisms in genetically susceptible individuals. Furthermore, exposure to these agents may be variable/modifiable or ubiquitous/unavoidable. In PBC, evidence for the importance of environmental factors to disease development is provided by low concordance in dizygotic (DZ) twins,⁴ differential geographical prevalence rates,^{4,15,16} seasonal differences in disease diagnosis,^{15,17} and occurrence of disease clustering.^{18,19} Several epidemiological studies performed over the past decade have identified family history, smoking, and history of urinary tract infection (UTI) as reproducible risk factors for PBC.^{20–28} In this review article, we will summarize current studies regarding environmental factors and their potential pathogenic mechanisms in PBC.

Geographical Location and Risk of Primary Biliary Cirrhosis

Prevalence of PBC is widely varied depending on geographical location, ranging from 1.91 to 40.2 per 100,000 inhabitants,²⁹ with the highest rates reported in the United States³⁰ and the United Kingdom (UK)³¹ and the lowest rates reported in Brunei Darussalam³² and Australia.³³ Although differences in case-finding methods, disease awareness, and access to health care may have somewhat confounded these studies, the prevalence disparities do suggest that environmental and/or genetic factors affect PBC. The composition of environmental agents (e.g., sunlight, chemicals, toxins, bacteria, viruses) present at specific geographical locations may influence development of autoimmunity. For instance, increasing latitude has been associated with risk of the auto-immune disease multiple sclerosis,³⁴ likely facilitated by decreased sunlight exposure and the immunoregulatory effects of ultraviolet radiation and vitamin D. Although this phenomenon could be at play in PBC pathogenesis, much more data would be required to convincingly show an effect as regional variability in HLA allele frequencies as well as dietary differences between populations could mask such an association.

Some of the earliest studies focusing on well-defined populations and suggesting a link between environmental factors and PBC came from the United Kingdom (UK) in the early and mid-1980s. In a study that noted high PBC prevalence in the heavily industrialized city of Sheffield in northern England, PBC was found to cluster within certain districts of the city; after considering many factors, a specific water reservoir was identified as the most likely source of a disease trigger.³⁵ Ensuing analyses found the implicated reservoir to have especially soft water and a lower concentration of fluoride compared with the other water

sources, although it remains unclear whether these differences would explain the disease cluster. In a subsequent study focused on the area surrounding the city of Newcastle-upon-Tyne, a large industrialized urban center in northeast England, a difference in disease prevalence was found between rural (3.7/100,000) and urban (14.4/100,000) populations.¹⁵ At the time, this finding was attributed as a likely difference in diagnosis rates as asymptomatic presentation was lower in areas outside of the primary urban center. However, this finding is also consistent with the contemporary view of a hygiene hypothesis affecting development of autoimmunity, which is some-what supported by a follow-up study in the region that again found risk of PBC to be higher in urban than in rural regions studied.¹⁶ It is important to note that neither of these studies directly report on the nature of daily activities and potential antigen exposures in the rural areas, so interpretation as evidence in support of a hygiene effect should be done with caution.

Although the UK studies suggest PBC rates and risks to be increased in more heavily industrialized areas, they do not explicitly implicate exposure to environmental pollutants/toxins as risk factors for PBC development. To directly address the question of whether environmental toxins affect PBC risk, a study was performed to examine the prevalence and potential clustering of PBC cases near Superfund toxic waste sites (SFSs) in New York City.¹⁹ These sites are heavily polluted with numerous chemical agents, including aromatic and halogenated hydrocarbons; residential proximity to these sites has been associated with immune dysfunction³⁶ and thyroid disease.³⁷ This study utilized cases from a comprehensive liver transplantation registry to avoid potential referral bias as well as a cohort of untransplanted patients followed at Mount Sinai School of Medicine (New York, NY) in their analysis and identified significant clustering of both groups near SFSs that were open-air dump sites.¹⁹ Although this study was unable to identify specific toxins influencing PBC risk, the authors speculated that exposure to volatile organic compounds (VOCs) such as benzene released from the site may contribute, especially considering the association of cigarette smoking (which contains numerous VOCs including benzene) with PBC and findings that halogenated forms of benzene can mimic the lipoylated autoantigen epitope found in PBC.³⁸

To test whether the environmental contributors to PBC development are static components of the environment or more transient in nature, the group from northeast England performed space-time clustering analysis on a cohort of 1,015 PBC cases diagnosed over 15 years and found statistical evidence for the phenomenon across the sample, with particularly strong clustering of patients diagnosed within 0.3 years of each other.³⁹ To follow up, the same group assessed seasonal variability of disease diagnosis in the cohort and found significant evidence for a sinusoidal presentation pattern with peak diagnosis occurring in June.¹⁷ These findings are important in that they suggest some environmental factors contributing to PBC are transient in nature and that disease latency prior to diagnosis might be relatively constant or the seasonal disease triggers may be quite strong. However, many potential environmental triggers for PBC exhibit seasonality, such as sunlight, infectious agents, pollution, exercise habits, and diet, thus limiting the interpretation of the findings.

Smoking and Risk of Primary Biliary Cirrhosis

The serious negative impacts of cigarette smoking on human health are well established. The first evidence that smoking might influence PBC development came from a questionnaire-based study of cases and controls from northeast England, in which 76% of PBC patients and 57% of controls indicated a history of smoking.²³ Subsequent studies of PBC in the UK and United States have universally replicated the association of smoking history (ever/never) with PBC development.^{22,24,27,28} A study from France found PBC to be associated with higher levels of exposure to cigarette smoke despite the case and control groups reporting similar rates of ever smoking.²¹ However, recent studies from Greece²⁶ and the Netherlands²⁰ did not identify any PBC association with smoking, although definitions and ascertainment did significantly differ from the other studies and overall rate of smoking in those populations was somewhat lower. An overview of the primary smoking data from these studies is provided in **Table 1**. In addition to an effect on PBC risk, smoking has been shown to impact severity of fibrosis in several chronic liver diseases^{40,41} including PBC.^{42,43} Specifically, smoking history and level of consumption were found to be significantly associated with advanced histological disease stage at presentation in two separate studies.^{42,43} Although there remains a paucity of data on how smoking effects disease progression postdiagnosis and in the context of treatment with UDCA, PBC patients should be encouraged to quit smoking.

Cigarette smoke contains thousands of components including nicotine, reactive oxidant substances (ROS), and polycyclic aromatic hydrocarbons, a great number of which are known mutagenic, carcinogenic, cytotoxic, or antigenic agents.^{44–47} The immunomodulatory effects of cigarette smoke are diverse and have been shown to include increases in pro-inflammatory cytokines interleukin- (IL-) 1, IL-6, IL-8, and tumor necrosis factor-(TNF-) α .^{48,49} The chronic inflammation and widescale cellular damage resulting from cigarette smoking can lead to a pathogenic adaptive Th1 immune response to various cellular antigens and disrupted regulatory T cell homeostasis.^{50,51} This is consistent with PBC, in which Th1 cells are the primary infiltrating lymphocytes and the regulatory function of the T cell compartment is diminished.^{52–54} However, the proinflammatory effect of smoking is not always stimulating, as cigarette exposure has been shown to suppress the activation of dendritic cells, which demonstrated decreased secretion of Th1 polarizing IL-12 and Th17 polarizing IL-23 in response to lipopolysaccharide (LPS) stimulation in vitro and ex vivo.⁵⁵ This finding may in part explain the increased susceptibility of smokers to several infectious agents, and also provide a mechanistic link (i.e., immuno insufficiency) between increased PBC risk attributed to smoking and UTI. In addition to the proinflammatory and immunosuppressive effects of cigarette smoking, halogenated forms of benzene found in cigarette smoke can mimic the lipoylated autoantigen epitope found in PBC.³⁸

Urinary Tract Infection and Risk of Primary Biliary Cirrhosis

The potential role of UTI in PBC was first reported in the mid-1980s in a study which noted that more PBC patients (19%) had evidence of significant bacteriuria compared with patients with other chronic liver disease (7%) and rheumatoid arthritis (8%).⁵⁶ Subsequent

prospective analysis of 144 consecutive PBC patients found that 35% developed UTI during follow-up, more than half of these infections were asymptomatic, and more than half of the bacteriuric patients had more than one infectious episode.⁵⁶ Follow-up studies were not able to identify additional factors explaining the increased prevalence of UTI among PBC patients⁵⁷ and antimicrobial treatment did not alter the natural history of infection in PBC patients.⁵⁸ As well, a second study of 160 consecutive PBC patients did not replicate the original association.⁵⁹ Questionnaire-based assessment in the major case-control studies of PBC also support a role for UTI in disease pathogenesis, with the majority finding that PBC patients significantly more often reported “ever having” UTI than controls (**Table 2**).^{21–23,27,28} In a recent U.S. study by Lammert et al, the reporting of ever having UTI did not significantly differ between case and control groups.²⁴ However, this study did find that PBC patients report having more “multiple UTIs” (defined as > one episode per year) than controls,²⁴ consistent with findings from the French study by Corpechot, which also reported more “recurrent UTI” (defined as > five episodes over lifetime) in PBC patients,²¹ and the original observational study.⁵⁶ Subsequent inquiries have found that the increased risk of UTI occurs primarily prior to and not after development of PBC,^{56,60,61} suggesting these infections may play a causative role in disease development and are not solely a consequence of the existing autoimmunity.

Escherichia coli (*E. coli*) is the predominant pathogen isolated from women with a UTI,⁶² and was recently shown to be a strong inducer of PDC-E2 specific AMA and liver pathology consistent with PBC in the NOD.B6 *Idd10.Idd18* mouse model,⁶³ indicating that infection with *E. coli* may indeed trigger PBC in a genetically susceptible host. In addition to *E. coli*, infection with the environmentally ubiquitous xenobiotic metabolizing bacteria *Novosphingobium aromaticivorans* (*N. aro*) has also been shown to induce AMA and PBC like disease in this same genetic model,^{63,64} providing evidence that infectious agents acting outside of UTI may also contribute to disease etiology. Indeed, several pathogens including *Helicobacter pylori*,⁶⁵ *Chlamydia pneumonia*,⁶⁶ *Mycobacterium gordonae*,⁶⁷ and Epstein-Barr virus (EBV)^{68,69} have demonstrated association with PBC in observational studies, although such findings have not been robustly reproducible.^{70–72} In a more recent study, PBC was associated with seropositivity for four common pathogens (*Toxoplasmosis gondii*, *Helicobacter pylori*, Cytomegalovirus, and EBV) and there was a high frequency of infection co-occurrence among PBC patients suggesting a role for infection burden (i.e., multiple infections) in PBC development.⁷³

Molecular Mimicry and Environmental Risk for Primary Biliary Cirrhosis

The loss of self-tolerance to PDC-E2 (and other 2-oxo-acid dehydrogenase complexes) is considered the initiating event leading to development of autoimmunity and subsequent biliary injury in PBC.⁷⁴ To break tolerance, weakly autoreactive B and/or T cells can be primed against cross-reactive epitope “mimics” under circumstances in which activation and proliferation rather than anergy is induced. This mechanism, termed *molecular mimicry*,⁷⁵ originally invoked viruses or bacteria as the mimic, but in concept has grown to include immunogenic alterations to self-proteins by environmental xenobiotics or other chemical toxins.⁷⁶ There is mounting evidence to suggest that molecular mimicry plays a key etiological role in PBC by facilitating loss of tolerance to PDC-E2 epitopes and development

of AMA. For instance, several mimicry peptides and proteins from bacteria commonly associated with PBC including *E. coli*, *N. aro*, and *Lactobacillus delbrueckii* have been shown to strongly cross-react with PDC-E2 AMA and activate T-cell clones from PBC patients,^{77–82} signifying that PBC could have arisen due to exposure to these antigens.

In addition to bacterial mimics, current evidence suggests that xenobiotics may play a crucial role in PBC pathogenesis, primarily through modification of the immunodominant inner lipoyl domain of PDC-E2.⁸³ Early studies demonstrated that patient sera reacted strongly against halogenated organic compound modified autoepitopes⁸⁴ and that immunization with such chemicals could elicit generation of AMA in an animal model.⁸⁵ Further investigation identified numerous xenobiotics with strong IgG reactivity against PBC sera, several of which were found to be more reactive than the native lipoylated PDC-E2 peptide and crossreactive with lipoic acid.³⁸ Among these compounds is 2-octynoic acid, a commonly used artificial flavoring and scent, which was subsequently shown to induce AMA and PBC-like disease in murine models.^{86,87} This finding is compelling in light of suggestive associations of PBC with frequent use of certain beauty products such as nail polish²² and hair dye,²⁸ although such epidemiological findings have been disputed.²¹ More recent work extending from the 2-octynoic acid findings suggest that a broad class of electrophilic drugs including acetaminophen and other commonly used nonsteroidal antiinflammatory drugs (NSAIDs) may contribute to the xenobiotic-induced mimicry and loss of tolerance to PDC-E2 seen in PBC.^{88,89} Of interest, transient AMA production has been reported in subsets of acute liver failure (ALF) patients, including those with acetaminophen toxicity,^{90,91} suggesting that severe oxidative damage of the liver can elicit development of AMA without conversion to frank autoimmunity. However, the nature of the genetic background (1) permissive for AMA development and (2) sensitive to subsequent autoimmunity remains obscure.

Antibiotics and Antigens: The Hygiene Hypothesis and Primary Biliary Cirrhosis

The Industrial Revolution and ensuing move toward mass production and increased specialization among the labor force fundamentally changed the structure of modern society, accelerating the growth and increasing the density of large urban centers. Subsequent development of modern approaches to public health including timely sanitation service, robust water treatment, and widespread use of vaccines and antibiotics have been greatly beneficial, supporting vast population growth, decreasing infant mortality, and increasing life expectancy in industrialized nations nearly fourfold in the past 150 years. However, as a trade-off, the diversity of foreign antigens to which we are exposed has drastically decreased, which may in part explain the recent epidemic of chronic inflammatory disorders such as allergy and autoimmunity by mechanisms proposed in the “hygiene” or more aptly the “old friends” hypothesis.^{92,93} This hypothesis posits that coevolution with microorganisms has shaped our immune system over thousands of years; as a result, exposure to a wide variety of pathogenic, environmentally ubiquitous but innocuous, and commensal organisms plays a key role in development and maintenance of the immunoregulatory program.⁹⁴ Numerous diverse mechanisms underlying this hypothesis

have been proposed as detailed in recent reviews,^{95,96} many of which are outside the scope of this article. However, loss of antigenic diversity as a mechanism facilitating autoimmunity driven by molecular mimicry and direct suppression of inflammation by helminth infection may be relevant to PBC and are discussed below.

Crossreactivity between the positively selected “weak-self” T-cell repertoire emerging from the thymus and the myriads of foreign antigens encountered throughout life forms the basis for discrimination of self from non-self and facilitates the ability to effectively clear pathogens while avoiding untoward immunity against beneficial commensal organisms and other sources of innocuous environmental antigens to which we are chronically exposed.^{97,98} This is accomplished by development and maintenance of homeostatic niches of effector and regulatory T-cell subsets with varied activation potentials in response to the quantity and quality of the priming antigenic exposures.^{99,100} As such, effective and specific immunity requires a highly diverse “exposome” (i.e., set of antigenic and chemical exposures),^{101,102} which has been significantly reduced in modern industrialized society. This loss of antigenic diversity could contribute to PBC by reducing the pool of induced regulatory T-cells weakly crossreactive with PDC-E2 self-epitopes that would normally provide the basis for peripheral control of autoimmunity, thus increasing the likelihood of autoimmune conversion as the result of molecular mimicry. As well, lower antigenic diversity could lead to ineffective immune responses leading to repeated exposure to potentially PDC-E2 mimicking pathogens (as encountered in UTI), an effect that may be even more pronounced in individuals harboring particular genetic variation contributing to diminished T-cell function.

In addition to diminished overall diversity in antigenic exposures as a potential mechanism underlying the hygiene hypothesis, individual components of the exposome that have been essentially eradicated in industrialized society are beginning to be implicated as major components of immunoregulation. Particularly among these are the helminths, a highly diverse group of multicellular metazoan parasites that have coevolved with mammals for millennia. Infection with helminths induces polarization toward a Th2 immune response, which is thought to be the evolutionary solution to engaging these macropathogens through limiting collateral damage to host tissue by classical Th1 inflammatory mediators and invoking repair mechanisms to simultaneously mend tissues and encapsulate the pathogens.¹⁰³ To avoid the immune response, helminths have evolved to directly modulate the immune system through induction of immunosuppressive programs resulting in stimulation of regulatory T-cells¹⁰⁴ and IL-10 secreting B-cells,¹⁰⁵ in effect modifying the Th2 response toward one that is generally more tolerogenic. Thus, the delicate balance between tolerance necessary to avoid unintentional damage to self and effective immunity to clear or mitigate the effects of pathogens was in part tuned by the endemic presence of helminth infection (extensively reviewed in¹⁰⁶). As such, near eradication of helminths in modern industrialized society may have left individuals prone to development of allergy or autoimmunity, depending on the extent of underlying genetic adaption. Evidence that this phenomenon might contribute to PBC was reported by a group from Japan, who evaluated 4,117 patients, including 105 with autoimmune liver disease (ALD), from three hospitals in Okinawa for infection with *Strongyloides stercoralis*, a common human parasitic helminth

endemic to the region.¹⁰⁷ Of interest, only 1% of the ALD group was found to be infected with *S. stercoralis* compared with 7% of controls ($p = 0.0063$). However, a significant cohort effect was described, suggestive of potential variation in exposure between men and women and incremental improvements in local hygiene. This prompted a subset analysis focused on women born prior to 1955, which found that of 60 PBC patients none were infected compared with 72 of 1,225 (5.9%) controls ($p = 0.045$), suggesting that *S. stercoralis* infection may indeed be protective against PBC.¹⁰⁷ Unfortunately, this study will be difficult, if not impossible, to replicate considering the rarity of helminth infection in current populations amenable to evaluation.

Concluding Remarks

The etiology of PBC is complex, driven by environmental exposure in the context of genetic background permissible for development of autoimmunity. Variation in geographical prevalence, presence of disease clustering, and seasonal differences in disease diagnosis provide evidence suggesting the role of environmental factors in PBC development may be important. However, despite several epidemiological studies, few potential disease triggers have been identified, with only cigarette smoking and UTI consistently found to be associated with disease. These associations and other suspected agents such as xenobiotics and microbes appear to influence PBC by facilitating molecular mimicry, leading to loss of tolerance to PDC-E2 and subsequent development of autoimmunity. However, other pathogenic mechanisms falling under the broad “hygiene hypothesis” may be involved and remain largely untested. The emerging availability of genome-wide datasets coupled with extensive questionnaire-based assessments of environmental exposure and access to comprehensive medical records of hundreds to thousands of PBC patients will allow us to begin interrogating the putative interaction between genes and environment contributing to PBC, incrementally improving our understanding of the underlying disease mechanisms and moving toward the ultimate goal of improved prognostication and therapy.

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Table 1

Smoking data from major epidemiological studies

Study	Year	Country	Subjects (% smokers)		Significance?	
			PBC	Controls	Ever smoke? ^a	Exposure level ^b
Howel et al ²³	2000	UK	100 (76%)	223 (57%)	OR 2.4	NA
Parikh-Patel et al ²⁷	2001	US	201 (66%)	141 (49%)	$p = 0.005$	NA
Gershwin et al ²²	2005	US	1032 (60%)	1041 (54%)	$p = 0.0034$	Sig. lower
Prince ²⁸	2010	UK	318 (NP)	2438 (NP)	OR 1.63	NA
			2258 (NP)		OR 1.57	
Corpechot et al ²¹	2010	France	222 (41%)	509 (42%)	NS	Sig. higher
Mantaka et al ²⁶	2012	Greece	111 (33%)	149 (37%)	NS	NA
Lammert et al ²⁴	2013	US	522 (53%)	616 (40%)	$p < 0.001$	Sig. higher
Boonstra et al ²⁹	2014	Netherlands	464 (20%)	128 (17%)	NS	NA

Abbreviations: NA: not assessed; NP, not provided; NS, not significant; PBC, primary biliary cirrhosis; UK, United Kingdom; US, United States.

^a Results provided as odds ratio (OR) or p values (P) as originally reported for the question “Ever smoke?”; definitions sometimes differed between studies.

^b Results reported for “level of exposure to smoking”; definitions varied between studies.

Table 2

UTI data from major epidemiological studies

Study	Year	Country	Subjects (% report UTI)		Significance?	Recurrent or Multiple ^b
			PBC	Controls	Ever UTI? ^a	
Howel et al ²³	2000	UK	95 (61%)	214 (51%)	OR 1.7	NA
Parikh-Patel et al ²⁷	2001	US	177 (70%)	133 (48%)	$p < 0.01$	NA
Gershwin et al ²²	2005	US	1032 (59%)	1041 (52%)	$p = 0.0003$	NA
Prince et al ²⁸	2010	UK	318 (NP)	2438 (NP)	OR 2.4	NA
			2258 (NP)		OR 1.7	
Corpechot et al ²¹	2010	France	218 (48%)	509 (31%)	$p < 0.0001$	$p < 0.0001$
Mantaka et al ²⁶	2012	Greece	NP	NP	NS	NS
Lammert et al ²⁴	2013	US	522 (39%)	616 (37%)	NS	$p < 0.001$
Boonstra et al ²⁹	2014	Netherlands	NA	NA	NA	NA

Abbreviations: NA: not assessed; NP, not provided; NS, not significant; PBC, primary biliary cirrhosis; UK, United Kingdom; US, United States; UTI, urinary tract infection.

^a Results provided as odds ratio (OR) or p values (P) as originally reported for the question "Ever had a UTI?"; assessments likely to have varied between studies.

^b Results reported for "Recurrent or multiple UTI"; definitions varied between studies.