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REVIEW

The immunological landscape of primary biliary cholangitis: Mechanisms and therapeutic prospects

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Abstract

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by the progressive destruction of intrahepatic bile ducts, leading to fibrosis, and potentially cirrhosis. PBC has been considered a prototypical autoimmune condition, given the presence of specific autoantibodies and the immune response against well-defined mitochondrial autoantigens. Further evidence supports the interaction of immunogenetic and environmental factors in the etiology of PBC. An immunological attack on biliary epithelial cells with secondary failure of biliary transporters, eg, the anion exchange protein 2, is traditionally considered the primum movens. A recent hypothesis proposes a primary failure of biliary epithelial cells with the downregulation of anion exchange protein 2 secondary to epigenetic mechanisms (miR-506 overexpression), which then triggers the immunological storm. This highlights the secretory defect as the culprit and sustaining factor in the pathogenesis of PBC with ursodeoxycholic acid helping to restore this protective mechanism by promoting bicarbonate secretion and reducing bile acid toxicity. In this review, we aim to provide the most recent evidence on the immunopathogenesis of PBC. We will analyze the immune function of the biliary epithelium, assessing the immunomodulatory functions of the bile acids and the evidence of the immunological roles of the secretory pathways targeted by the current treatments.

Keywords: autoimmunity, cholangiocyte, cholestasis

Abbreviations: AMA, antimitochondrial antibody; BEC, biliary epithelial cell; DC, dendritic cell; FXR, farnesoid X receptor; GWAS, genome-wide association studies; HLA, human leukocyte antigen; IFN-γ, interferon-gamma; isoDCA, 3β-hydroxydeoxycholic acid; MAIT, mucosal-associated invariant T; MHC, major histocompatibility complex; miRNA, micro RNA; PBC, primary biliary cholangitis; PDC-E2, E2 component of mitochondrial pyruvate dehydrogenase complex; pIgR, polymeric immunoglobulin receptor; PPAR, peroxisome proliferator-activated receptor; TLR, toll-like receptor; Treg, regulatory T cell; T_{RM}, tissue-resident memory cell; UDCA, ursodeoxycholic acid.

Vincenzo Ronca and Scott P Davies contributed equally to the production of the manuscript.

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INTRODUCION. WHERE ARE WE COMING FROM AND WHERE WE ARE GOING: UNSOLVED QUESTION IN THE PATHOGENESIS OF PRIMARY BILIARY CHOLANGITIS

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by the progressive destruction of intrahepatic bile ducts, lesecading to cholestasis, fibrosis, and potentially cirrhosis. PBC demonstrates a striking female-to-male ratio of approximately 9:1 and, as such, predominantly affects middle-aged women.[1]

Historically, PBC has been considered a prototypical autoimmune condition, possessing both clinical and biochemical features of autoimmunity. Using complement fixation, Ian MacKay was the first to describe autoantibodies reacting against the human liver and kidneys in patients with PBC. In 1965, Doniach and Walker were the first to confirm the presence of autoantibodies by immunofluorescence, reporting an unusual pattern in the serum of PBC patients showing reactivity with mitochondrial proteins.[2,3] These autoantibodies became known as anti-mitochondrial antibodies (AMA). Several reports confirmed Doniach and Walkers data, whilst also showing the sensitivity (approximately 90%–95% of patients with PBC) and specificity of these proteins, thus making them a valuable diagnostic tool for PBC.[4]

Understanding of the PBC immune response made a significant step forward with the identification and characterization of the enzymes targeted by the autoantibodies; the 2-oxo acid dehydrogenases located on the inner aspect of the mitochondrial membrane. This protein, the E2 component of mitochondrial pyruvate dehydrogenase complex (PDC-E2), was subsequently cloned by Gershwin et al in 1987.[5,6] The identification of PDC-E2 as the primary target of AMA was a significant milestone, providing insights into the autoimmune response driving PBC. The immunodominant epitope recognized by T cells and B cells is PDC-$E2_{163\text{-}176}$, which resides in the lipoyl domain of the PDC-E2 protein. The aberrant production of antigen-specific autoantibodies, the hallmark of the B-cell reactivity against the autoantigen, is the defining foundation for an autoimmune condition. Histological data of PBC livers showed PDC-E2-specific T cells enriched around the bile ducts and hilar lymph nodes, which reinforced the hypothesis that PBC is in fact a prototypical autoimmune condition.[7–9] Other clues on the autoimmune hypothesis were certainly the striking female preponderance and the recurrent disease after transplantation, with the recurrent disease reducing significantly the graft survival (32275981).

Despite the supposed autoimmune nature of PBC, steroids and other immunosuppressants have failed to control the disease progression, with patients frequently developing cirrhosis and liver failure.[10–14] A turning point in the history of PBC treatment was offered by the introduction of ursodeoxycholic acid (UDCA) in 1987, which entirely changed the life expectancy of all responder patients.[15–19] The success of this treatment, alongside the failure of the immune-targeted drugs, certainly raises more questions about PBC pathogenesis. Beuers' and Banales' groups introduced a new angle in the PBC pathogenesis, reversing the expected chain of events; they suggested that the loss of immune tolerance follows an increased apoptotic stimulus in biliary epithelial cells (BECs) due to a secretory defect.[20–28] They highlighted the role of the epigenetic downregulation of the Cl^-/HCO_3^- anion exchanger 2 in BECs. The direct effect is the impairment of the bicarbonate-rich "umbrella" that protects the biliary epithelium from bile acid toxicity, leading to apoptosis and inflammation. Although this defect was originally suggested by work conducted in the late 90s,[29,30] these later works highlighted the secretory defect as a direct sustaining factor in the pathogenesis of PBC. To reinforce the key role of the bicarbonate umbrella in PBC, the authors demonstrated that UDCA helps restore this protective mechanism by promoting bicarbonate secretion and reducing bile acid toxicity, offering insights into the nonimmune mechanisms driving PBC.[20,21,25–28]

In Figures 1 and 2, we offer a timeline of the major discoveries in PBC pathogenesis to demonstrate the switch of focus in the basic and translational research for this disease. A unifying hypothesis that can effectively unite the 2 angles is yet to be offered and proven. In fact, several critical questions about the pathogenesis of PBC remain unresolved. For instance, the initial triggers that lead to the loss of immune tolerance and the development of autoimmunity against PDC-E2 are not fully understood. Furthermore, the striking female preponderance and recurrence of the disease after transplant remain as intriguing factors. Both are yet to be explained due to lacking data beyond speculation.

The immunological hypothesis is widely accepted as an accurate representation of the early stages of PBC pathogenesis. Despite this, these patients are often unresponsive to immunosuppression, a topic that remains a source of interest and puzzlement. In contrast, current treatments that have their main effect on the secretory pathway, like UDCA, obeticholic acid, and peroxisome proliferator-activated receptor (PPAR) agonists, can slow disease progression, suggesting a more prominent role of these pathways in the pathogenesis of PBC. This last year has been rich with crucial publications regarding PBC, both on clinical and experimental aspects of the disease, and with great interest surrounding the immune system once again. In this review, we will provide the historical and most recent evidence on the immunopathogenesis of PBC.

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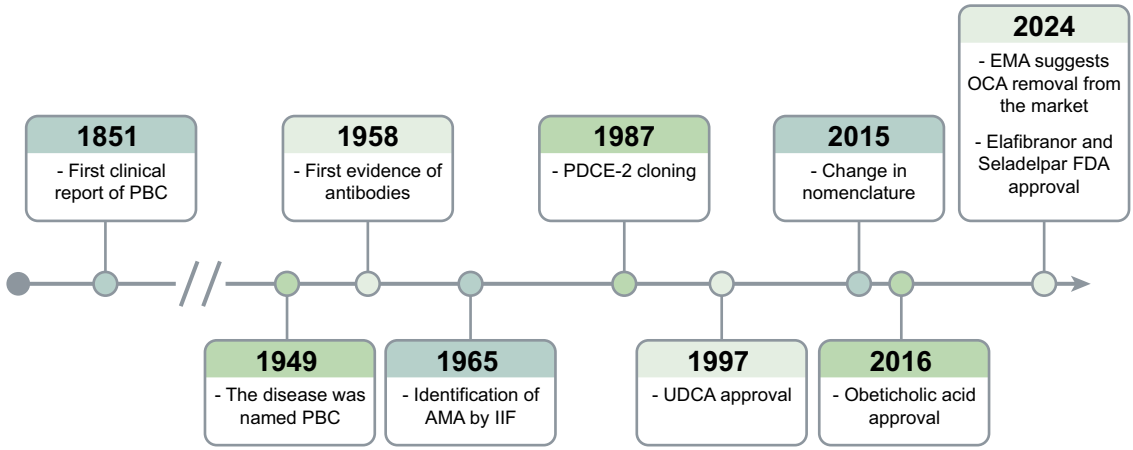

FIGURE 1 A timeline of the main events in the history of PBC. Abbreviations: AMA, anti-mitochondrial antibodies; EMA, European Medicines Agency; FDA, Food and Drug Administration; IIF, indirect immunofluorescence; OCA, obeticholic acid; PBC, primary biliary cholangitis; PDC-E2, E2 component of mitochondrial pyruvate dehydrogenase complex; UDCA, ursodeoxycholic acid.

We will also analyze the immune function of the biliary epithelium, assessing the evidence of the immunological roles of the secretory pathways targeted by the current treatments. Finally, we will summarize the relatively recent evidence of the immunomodulatory functions of bile acids.

DISEASE ONSET: GENETIC PREDISPOSITION AND ENVIRONMENTAL FACTORS

PBC is driven by a complex interplay between genetic predisposition and environmental factors. It is considered a complex genetic trait, with multiple genetic variants contributing to disease susceptibility. Familial clustering highlights the heritable component, as the risk is substantially higher in first-degree relatives, with a relative risk (λ_s) of 9.13 to 10.5 compared to more distant relatives.[31–34] Twin studies reveal a 63% concordance rate among monozygotic twins, indicating a significant genetic contribution.[31] Genome-wide association studies (GWAS) have identified several loci conferring either protection or risk to developing the disease. The strongest association remained with the human leukocyte antigen (HLA) region on chromosome 6, although this was proportionally lower compared with other autoimmune conditions.[35,36] In European populations, HLA-DRB1*08 is strongly associated with an increased risk of PBC, while HLA-DRB1*11 and HLA-DRB1*13 are protective alleles. In Japanese cohorts, HLA-DRB1*0803 is a key risk allele, whereas HLA-DQB1*0301 offers protection in Chinese populations, demonstrating the ethnic variability in genetic predisposition.[37–42]

More than 50 non-HLA variants have also been identified as associated with PBC, offering insights into the biological pathways involved in its pathogenesis.[36,43,44] According to pathway-based analyses, these loci are associated with signals involved in the immune response, particularly immune regulation, antigen presentation, B cell activation, and lymphocyte differentiation. These genetic studies outline a landscape of PBC that points toward the architecture of an autoimmune disease. In support of this, most of these loci are shared with other autoimmune conditions.[45]

The IL-12 signaling pathway emerges as a strongly associated factor with PBC according to GWAS results. IL-12 production is generally upstream of the immune cascade, largely being produced by antigen-presenting cells. It subsequently induces naïve T cell (T helper 0; T_H0) commitment toward the T_H1 lineage of $CD4^+$ T cells and the production of interferon-gamma (IFN-γ). In relation, chronic expression of IFN-γ induces autoimmune cholangitis in the ARE-$Del^{-/-}$ mouse model, which resembles other features of PBC, namely female preponderance and AMA production.[46] Additionally, IL12p40 knockout in mice possessing T cells expressing the dominant negative form of TGF beta-receptor restricted to T cells model attenuated autoimmune cholangitis, reinforcing the importance of IL-12 and IFN-γ in the immunology of PBC.[47] IL-12-IL-12R binding activates two kinases, JAK2 and TYK2, which phosphorylate STAT4. Concordantly, gene variants in loci of both STAT4 and TYK2 have been found associated with PBC susceptibility.[48–50] Moreover, IL12p40 can dimerise with IL12p19 to form IL-23, a cytokine which feeds the T_H17 pathway, another key pathway in PBC pathogenesis.[51,52] Finally, another important loci includes C-C chemokine ligand 20 (CCL20), which influences the recruitment of T_H17 and $CD8^+$ cells to the bile ducts, contributing to the immune-mediated destruction of biliary epithelium.[51,53–56]

The role of the exposome has been further highlighted by the strong HLA loci association with PBC risk.

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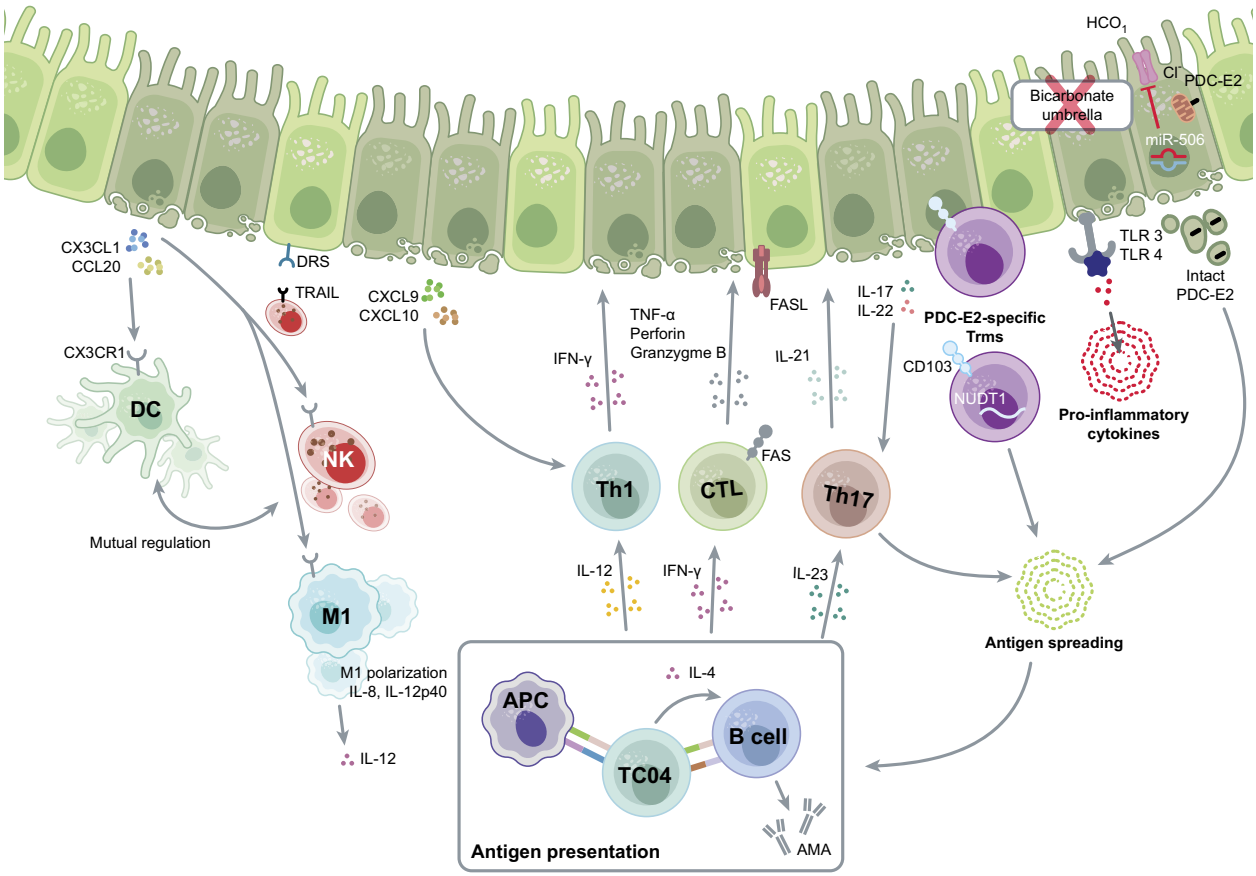

FIGURE 2 Pathogenesis of primary biliary cholangitis. Central to disease initiation is the presentation of the autoantigen PDC-E2 on the surface of apoptotic blebs, which stimulates the proliferation of autoreactive B-cell clones and the production of AMAs. Biliary epithelial cells in PBC exhibit increased surface expression of Toll-like receptors TLR4—responsive to bacterial lipopolysaccharide—and, particularly in early stages, heightened gene expression of TLR3, which senses viral double-stranded RNA. Activation of biliary epithelial cells via these TLRs leads to the release of proinflammatory cytokines and chemokines, further disrupting immune tolerance. Chemokines such as CX3CL1 (fractalkine) and sphingosine-1-phosphate promote chemotaxis and M1 polarization and circulating monocytes, resulting in the production of proinflammatory cytokines like IL-8 and IL-12p40. Elevated levels of CX3CL1 from biliary epithelial cells increase the frequency and cytotoxic activity of natural killer (NK) cells, enhanced by increased expression of TRAIL and perforin. CCL20 and CX3CL1 attract immature dendritic cells to sites of inflammation, where they release high levels of nitric oxide (NO). T-cell responses are pivotal in PBC pathogenesis, with early-stage disease characterized by a Th1-like response and late-stage disease by a Th17-like response. The ensuing inflammation impairs bicarbonate secretion, reducing the protective lining of the biliary epithelium. Additionally, overexpression of microRNA-506 (miR-506) leads to post-transcriptional downregulation of the anion exchanger 2, further compromising epithelial protection. Resident memory T cells are the main autoreactive population within PBC livers, characterized by increased expression of nucleoside diphosphate X hydrolase 1. The activation of Trms and their chronic stimulation causes their innovation into biliary epithelial cells, inducing apoptosis and spreading the antigen. Abbreviations: AMA, anti-mitochondrial antibody; APC, antigen-presenting cell; CTL, cytotoxic T cell; DC, dendritic cell; DRS, death receptors; FASL, Fas ligand; IFN-γ, interferon-gamma; NK, natural killer; PDC-E2, E2 component of mitochondrial pyruvate dehydrogenase complex; Th1, T-helper 1; TLR, toll-like receptor; TRAIL, TNF-related apoptosis-inducing ligand.

There are several proposed associations that might play a role in tolerance disruption. There is a strong association between recurrent urinary tract infections and PBC.[57] Bacterial pathogens, such as *Escherichia coli* and *Novosphingobium aromaticivorans*, are thought to contribute via molecular mimicry. This occurs where bacterial proteins structurally resemble PDC-E2, which consequently provokes cross-reactivity from the immune system, precipitating inflammation and bile duct destruction.[58–64] The geographical clustering of PBC cases in certain regions also supports the hypothesis that environmental factors play a role, including local species of bacterial gut flora and pathogens.[65]

Xenobiotics, such as 2-octynoic acid—found in cosmetics and food additives—have been implicated as environmental triggers for PBC. These compounds have been shown to modify PDC-E2 and enhance its immunogenicity, triggering autoimmune responses in genetically predisposed individuals.[66] Experimental models have demonstrated that mice exposed to 2-octynoic acid develop PBC-like symptoms, including the production of AMAs and bile duct damage, reinforcing the link between environmental exposure and disease

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onset.[67] Additionally, exposure to volatile organic compounds and aromatic hydrocarbons—commonly found in cigarette smoke and near toxic waste sites—have been linked to an increased risk of PBC.[60] These toxins may mimic autoantigens or modulate immune responses, further contributing to immune dysregulation and the breakdown of self-tolerance.

Epigenetic factors bridge the gap between environmental influence and the genetic architecture of PBC. The first evidence of epigenetic dysregulation in PBC came from our lab when we demonstrated that peripheral $CD4^+$ T cells in PBC patients had a significant reduction in methylation of the cluster of differentiation 40 L (CD40L) promoter in PBC patients and, in turn, increased CD40L expression.[68] Similarly, we demonstrated hypomethylation of the promoter of CXCR3, a key chemokine for leukocyte trafficking, including T cells and NK liver homing[56,69–71] in PBC patients.[72] Consequentially, we observed increased protein expression in the liver and peripheral blood of PBC patients compared with controls.[72]

Traditionally, GWAS have focused on autosomes, often excluding X chromosome (ChrX) due to its complex inheritance patterns. However, ChrX makes significant contributions to immune-related functions. Recent research has identified genetic loci on ChrX that are linked to PBC.[73] One such locus, marked by the rs7059064 polymorphism, which encompasses several immune-related genes, was shown to be significantly related to PBC. Notably, rs7059064 includes a super-enhancer that regulates key immune genes like FOXP3, crucial for regulatory T-cell function.[73] Additionally, epigenetic mechanisms, including histone modifications and enhancer RNA production, associated with PBC patients further suggest that super-enhancers on ChrX might influence immune dysregulation. The study also found significant enrichment in differentially methylated genes in PBC, linking ChrX epigenetics to disease susceptibility. Additionally, the authors found a notable enrichment of circular RNAs in PBC-associated regions, and one specific circular RNA, hsa_circ_402458, was found dysregulated in patients with PBC, potentially contributing to chronic inflammation by interacting with micro RNA (miRNA)s.[73] These findings suggest that epigenetic modifications on ChrX, particularly affecting immune-related genes, may partly explain the female predominance in PBC by contributing to immune dysregulation and disease susceptibility.[36,73,74]

Noncoding RNAs have been of great interest in the pathogenesis of PBC, especially concerning small noncoding RNAs (miRNAs) which can regulate protein expression by translational repression or mRNA destabilization.[75] Despite a long list of deregulated miRNAs in PBC, miR-506 stands out as the most noteworthy; miR-506 prevents the translation of anion exchange protein 2 mRNA, leading to impaired bicarbonate secretion, increased cellular stress, and susceptibility to bile acid toxicity. This was shown to increase BEC apoptosis and, in turn, cause tolerance breakdown.[21,24] Additionally, miR-21 has been implicated in promoting necroptosis, with elevated levels observed in PBC livers. Furthermore, inhibition of miR-21 in mouse models of cholestasis was shown to ameliorate liver damage by targeting cell death pathways. Overall, these studies suggest that miRNAs may offer potential therapeutic targets in PBC.[76,77]

Last year, You Li and colleagues provided significant mechanistic insight from GWAS findings related to PBC.[78] They pinpointed a regulatory variant within the 19p13.3 locus, identifying an intronic SNP rs2238574 within the gene encoding AT-rich interaction domain 3A (ARID3A) as a potential causal factor for the disease. This SNP's risk genotype was found to increase enhancer activity, thereby elevating ARID3A expression by altering the DNA-binding affinity of key transcription factors in myeloid cells. Epigenetic profiling revealed marked enrichment of active enhancer signatures in the rs2238574-containing region in human $CD14^+$ monocytes but not in $CD19^+$ B cells, $CD4^+$ T cells, or $CD8^+$ T cells. This led the authors to propose that this region functions as a myeloid cell-specific enhancer. Functional analyses revealed that transcription factors, such as PPARγ, NR2F1, and NR2C2 preferentially bound to the risk allele of rs2238574, contributing to increased ARID3A expression.[78] This was consistent with experimental data in PBC which demonstrated how $CD68^+$ monocytes/macrophages accumulate around damaged bile ducts.[79] Those derived from PBC patients exhibit increased sensitivity to infectious stimuli by secreting cytokines and chemokines that intensify immune responses and exacerbate BEC injury compared with healthy controls.[79,80]

The predisposition to develop autoimmunity is arguably due to unbalanced immunotolerance. A reduction in the functionality or number of regulatory T cells (Tregs) is often considered, and PBC is not an exception to this paradigm. In fact, data from models of PBC support Treg deficiency as being an early defect that precipitates PBC pathogenesis. More specifically, the dnTGF-βRII murine model mimics the PBC histology damage, through the accumulation of tissue-specific autoreactive T cells. This model relies on selectively knocking down the TGF-βR-signaling pathway in T cells, which directly affects Treg suppressive capacity.[81] Other mouse models with perturbed Treg development, like in Scurfy mice or IL-2Rα knockouts, develop autoimmune cholangitis with AMA production in 100% of individuals.[82,83] Furthermore, Liaskou et al demonstrated Treg lineage instability within an inflammatory environment, showing significant increases in IFN-γ expression by Tregs on exposure to low levels of IL-12 leads.[84] In relation, adoptive transfer from Treg from WT C57BL/6 mice to a model of autoimmune

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cholangitis, but not from dnTGF-βRII, successfully reduced portal inflammation, as shown by Tanaka et al.[85] This study not only suggested the potential of autologous Treg cell-therapy in the treatment of PBC, but further confirm the reduced functionality of Tregs in PBC murine models.

In summary, PBC is a multifactorial disease driven by genetic susceptibility, particularly within HLA and non-HLA loci, and is exacerbated by environmental factors. Together, these elements contribute to immune dysregulation, biliary injury, and the chronic inflammation that defines PBC (Figure 2).

THE TARGET: HOW BECs CONTRIBUTE TO DISEASE PATHOGENESIS

The biliary epithelium is the ultimate target of pathological processes in PBC. When exposed to an inflammatory insult, BECs become activated and start proliferating to compensate for the loss of biliary cells, while also sustaining secretory functions.[86,87] Under chronic damage, however, the cellular loss might outpace the regeneration and causing the ductopenia, a common histological finding in PBC patients. The cellular turnover in chronic cholestatic is partially mediated via apoptosis, as witnessed by the increased DNA fragmentation in PBC patients-derived BECs compared with controls.[88] Several processes have been attributed to this observation in PBC; death receptor 5 (TRAILR2) is increased on the surface of BECs from patients with PBC. Takeda and colleagues demonstrated that activating this receptor not only induced apoptosis but precipitated chronic cholestatic damage.[89] Increased oxidative stress is an additional process recognized to induce apoptosis in BECs in PBC.[90] Of note, failure in clearing cellular debris and apoptotic blebs is recognized as a risk factor for developing autoimmunity.[91,92] Concordantly, a less effective function of macrophages as scavengers of opsonized apoptotic cells has been shown in PBC compared with controls.[93]

Further advances in the field provide more avenues in which cell death among BEC would be promoted. More recently, our group described a heterotypic cell-in-cell structure whereby $CD8^+$ T cells invade BECs.[94] Although not unique to cells and tissue derived from patients with PBC, we documented the presence of $CD8^+$ within cytoplasmic spaces of BEC in 100% of patient samples analyzed, including biopsies acquired from patients and varying stages of diagnosis. Furthermore, Zhao et al[95] have shown that these events, which we uncovered as generated through an avesicular form of entosis (AVentosis), correlated with increased apoptosis within BEC.

According to the secretory hypothesis, primary defects in the BEC secretome could arguably be the initial culprit and a sustaining factor for cholestasis, and therefore inflammation, of the biliary epithelium. Diminished anion exchange protein 2 expression consistently observed in both liver tissue and peripheral blood mononuclear cells of PBC patients leads to increased intracellular pH in BECs.[96,97] This imbalance activates soluble adenyl cyclase and promotes bile salt-induced apoptosis of BECs. However, BECs themselves have also demonstrated an active role in inflammation. They express various toll-like receptors (TLRs) that recognize pathogen-associated molecular patterns and damage-associated molecular patterns. On activation, TLRs initiate signaling pathways that result in the secretion of proinflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α, which amplify local inflammation and recruit additional immune cells to the site of injury.[79,98,99] TLR3 expression is upregulated in the portal tracts of patients with early-stage PBC, where it is strongly associated with type I interferon production, implicating this pathway in the disease's pathogenesis.[100] Increased expression of the lipopolysaccharides receptor, TLR4, by BEC, has also been reported in PBC.[101] Additionally, BECs exposed to bacterial CpG DNA, a ligand for TLR9, show enhanced production of anti-mitochondrial antibodies (AMAs), linking TLR signaling to the autoimmune features of PBC.[102]

BECs also undergo cellular senescence in response to chronic injury, which is characterized by permanent cell cycle arrest and the acquisition of a senescence-associated secretory phenotype. This phenotype includes the hypersecretion of proinflammatory and profibrotic molecules, such as CX3CL1, CCL20, IL-6, and interferons, which further contribute to inflammation and fibrosis in PBC.[103–106] As such, senescent BECs accumulating in damaged bile ducts may function as recruiters of monocytes and lymphocytes, which express corresponding receptors of the chemoattractant molecules they secrete.[107] Additionally, impaired phagocytic function of senescent BECs leads to the accumulation of apoptotic cells, exacerbating peribiliary inflammation.

What is clear now is that, either through impaired secretory function or direct involvement in immune responses, BECs are indeed part of the pathogenetic process. What remains unknown is the chain of events precipitating cholestasis and inflammation and, even more so, which one of these 2 processes is the culprit. Li and colleagues proposed a novel model of disease that would explain both the organ specificity of the disease and the precipitating events in the biliary damage. They recently identified a unique type of $DUOX2^+$ $ACE2^+$ small BEC population as a key factor for bile secretion and proposed them as the pathogenic target in PBC.[108] They also showed that hepatic polymeric immunoglobulin receptor (pIgR) is highly expressed in this BEC subtype and that the levels of anti-pIgR antibodies are increased in patients with PBC. On this ground, they speculated that the existence of

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IgA transcytosis mediated by the pIgR in DUOX2$^+$ ACE2+ small BECs leads to pIgR antigen presentation to immune cells. Subsequently, this loss of tolerance induced pIgR-specific humoral and T-cell autoimmunity, which drove the production of anti-pIgR autoantibodies. This further leads to the recruitment of pIgR antigen-specific CD27$^+$ memory B and plasma cells to the hepatic portal tracts. The elevated levels of anti-pIgR autoantibodies, together with other antigen-specific autoantibodies, further damaged DUOX2$^+$ ACE2$^+$ small BECs in the small bile ducts. This impaired bile secretion and contributed to the development of PBC, even if patients failed to develop AMA-M2 antibodies.[108] In conclusion, BECs are integral to the pathogenesis of PBC, not only as targets of immune-mediated damage but also as active contributors to the disease process. Through dysregulated ion transport, immune signaling, apoptosis, and cellular senescence, BECs play a pivotal role in chronic inflammation and tissue damage that is characteristic of PBC. Understanding these mechanisms offers potential therapeutic targets aimed at restoring BEC function and mitigating the disease's progression.

ANTIGEN PRESENTATION IN PBC

The adaptive immune response is considered to primarily drive the immune attack of the biliary epithelium in PBC. Antigen presentation in the liver is a uniquely controlled process in which homeostasis favors immune tolerance. This is an adaptation to the overload of food antigens coming from the portal circulation, including new antigens derived from the xenobiotic metabolism, that the liver is exposed to. This environment is maintained by a variety of liver-resident antigen-presenting cells, including dendritic cells (DCs), Kupffer cells, liver sinusoidal endothelial cells, and even hepatocytes. Under normal conditions, antigen presentation by these cells, due to either immature phenotype or low expression of co-stimulatory molecules and major histocompatibility complex (MHC)-II, leads to unsuccessful T-cell activation. This promotes Treg maturation, which further contributes to maintaining immune homeostasis.[94,109–113] This tolerance is essential, given the liver's constant bombardment of antigens from the gut through the portal circulation.

Beyond the paradox of PBC, which is developing an autoimmune response in a tolerogenic organ like the liver, another challenge lies in understanding how organ-specific immune targeting is driven by PDC-E2, a protein that is widely expressed across tissues. In inflammatory conditions, PDC-E2 is upregulated in BECs and, as Odin et al demonstrated, it remains present on the surface of apoptotic BECs.[114] Under normal circumstances, the binding of glutathione to sulfhydryl groups in apoptotic cells neutralizes the immunogenicity of PDC-E2.[114] However, in PBC, this process is defective, leaving PDC-E2 exposed on the surface of BECs. Our group has further identified the persistence of this immunogenic antigen on apoptotic blebs, making it accessible for recognition by AMAs. The dissemination of this autoantigen within the hepatic environment triggers and sustains inflammation. In vitro studies have demonstrated that macrophages responding to AMA-antigen complexes release proinflammatory cytokines, including IL-6, TNF-α, and IL-12, thereby contributing to the amplification of the immune response.[8,115,116]

The combination of antigen persistence and aberrant stimulation, along with continuous macrophage-driven inflammation, is thought to underlie granuloma formation, a relatively common histopathological finding. These non-necrotizing granulomas, enriched with CD163$^+$ CD68$^+$ macrophages, follicular dendritic cells, fibroblasts, and B cells, are observed in approximately 4% of patients with PBC,[117] although a recent study observed these structures in over 60% of their cohort.[118] Interestingly, these structures share similarities with tertiary lymphoid follicles, which form in nonhematopoietic tissues and are typically located around damaged bile ducts. Within these follicles, B cells are centrally positioned and surrounded by T cells, suggesting that these granulomas function as ectopic lymphoid organs, serving as cytokine hubs and T-cell priming sites, driven by persistent antigen exposure.[119] Supporting this hypothesis, Krausgruberg et al demonstrated that CD8$^+$ T-cell priming by hepatic dendritic cells (DCs) occurs independently of CCR7, a chemokine receptor required for DC migration to lymph nodes, indicating effective local antigen presentation.[120] These liver tertiary lymphoid follicles have also been shown to form within the dnTGFβRII mice.[118] Importantly, inhibition of sphingosine-1-phosphate signaling prevented tertiary lymphoid follicle formation and alleviated cholangitis in these mice.

Notably, these granulomas express markers such as CD1d and CD11c, characteristic of dendritic cells. Emerging evidence highlights the regulatory role of hepatic DCs in liver diseases, with various DC subpopulations displaying distinct capacities to promote either immunity or tolerance. In the context of PBC, hepatic CD103$^+$CD11b$^-$ cDC1 cells have been identified as a key subset involved in disease pathogenesis. These cells are located exclusively within the portal areas of the liver, both in experimental models of autoimmune cholangitis and in human PBC, suggesting a strategic positioning for sampling antigens.[121] Their proximity to bile ducts allows them to capture antigens from the biliary epithelium, which is likely central to the immune dysregulation observed in PBC.

It is still debated whether BEC can actively and effectively present antigens themselves. They constitutively express MHC-I molecules and, on stimulation,

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can aberrantly express MHC-II molecules, theoretically allowing them to present antigens to $CD4^+$ T cells. This MHC-II expression is notably increased in conditions associated with immune-mediated bile duct damage, such as PBC.[122–124] However, the lack of co-stimulatory molecules expressed on BEC, such as CD28 and CD3, would limit the ability of BEC to effectively activate T cells through antigen presentation. In vitro functional assays have shown less potent activation power, compared with liver sinusoidal endothelial cells.[125]

Recent studies have also shown that BECs can present lipid antigens to, and therefore activate unconventional T cells. This includes natural killer T cells, which they can present via the nonpolymorphic MHC homolog, CD1d. CD1d is expressed by normal biliary epithelium but downregulated in various liver diseases, including PBC.[126] Additionally, BECs can present antigens to mucosal-associated invariant T (MAIT) cells, which are enriched in the liver and intestine. In PBC, MAIT cells, known as the "biliary firewall," are found around bile ducts and express chemokine receptors CCR6 and CXCR6, as well as the E-cadherin receptor integrin $\alpha E\beta 7$ (commonly referred to as CD103), enabling their migration and localization to the peribiliary region in response to CCL20 and CXCL16 secreted by BECs.[127]

THE LIVER CHOLESTATIC MICROENVIRONMENT AND HOW IT SHAPES THE IMMUNE RESPONSE

We explored the reduced protective function of BECs in PBC, focusing on the malfunctioning bicarbonate barrier. While this suggests a direct harmful impact of bile acids on the biliary epithelium, recent research has connected bile acids with immune responses, indicating a direct role of bile acids in shaping immunity.

Cholestasis is defined as an impairment of bile flow or secretion. This can be due to extrahepatic or intrahepatic conditions but ultimately results in changes to hepatic bile acid plethora.[128,129] Furthermore, intrahepatic and plasma bile acid concentrations rise, and fewer bile acids reach the intestines, limiting their modification by the gut microbiome. Coupled with disrupted hepatic bile acid synthesis,[130] this leads to altered bile acid composition and localization. In early-stage PBC, compared with healthy controls, an increase in taurine-conjugated chenodeoxycholic acid, the major hydrophobic bile acid in humans, has been described, with a shift in conjugation patterns favoring taurine over glycine conjugates rather than a change in overall bile acid composition.[131]

Changes in the bile acid pool impacts the immune system and contributes to disease progression.[132] The increased bile acid levels cause inflammation through direct damage to the hepatocytes, which subsequently causes the release of High-Mobility Group Box 1 protein. High-Mobility Group Box 1 acts as a damage-associated molecular pattern, triggering the secretion of TNF-α and IL-6, by binding to TLR4 and thereby amplifying inflammation.[133] Additionally, exposure to taurine-conjugated CA causes increased transcription of genes for cytokines and adhesion molecules in hepatocytes of murine model, including MCP1 (CCL2), MIP2 (CXCL2), and ICAM-1.[134] These changes suggest involvement in neutrophil chemotaxis, justifying the increased neutrophil infiltration observed in bile duct ligation models that is directly related to an increased in ICAM-1 expression. To prove the direct involvement of adhesion molecules, Gujral et al demonstrated a striking reduction of neutrophil in ICAM-1-deficient mice undergoing BDL, with a consequential reduction in ROS production and hepatocyte loss.[135] This is consistent with what is observed in patients with PBC, which often exhibit increased levels of soluble ICAM-1 in plasma.[136] Additionally, bile acids have been linked to increased expression of MHC-I on hepatocytes and BECs,[137] potentially enhancing antigen presentation and activating $CD8^+$ T cells.

The impact of bile acids on adaptive immunity has recently become more evident. Hang and colleagues described the effect of 3-oxo-lithocolic acid (LCA) and isoallo-LCA, 2 metabolites of LCA, as impacting T_H17 – Treg balance. They further revealed that 3-oxo-LCA directly binds RORγt and inhibits T_H17 differentiation of $CD4^+$ T cells, while isoallo-LCA stimulated Treg differentiation by promoting mitochondrial ROS production and, in turn, enhancing the expression of FOXP3.[138] Accordingly, feeding the mice with these 2 metabolites reduced the T_H17/Treg ration in the ileal lamina propria. The bile acid composition in the gut, and consequently in the liver, is highly dependent on microbial bile acid metabolism, which has been linked to adaptive immunity.[139] Song and colleagues showed that gut bile acid composition can be affected by both dietary elements and microbial factors. They found that secondary bile acids acting on vitamin D receptors modulate a specific population of $FOXP3^+$ Treg cells which express RORγ ($ROR\gamma^+$ Treg cells) and are critical for maintaining immune homeostasis in the colon. The significance of this bile acid-VDR signaling axis was demonstrated in mice lacking VDR, which were more susceptible to dextran sulphate sodium–induced colitis.[140] Recently, Campbell et al reported that 3β-hydroxydeoxycholic acid (isoDCA), a low-abundance secondary bile acid, significantly enhances the differentiation of peripherally induced Treg cells;[141] isoDCA promoted FOXP3 induction by reducing the immune-stimulatory activity of dendritic cells through the involvement of isoDCA-farnesoid X receptor (FXR) signaling. A microbial consortium producing isoDCA was shown to increase $ROR\gamma^+$ Treg cell numbers in the colon. Furthermore, bile acid-driven activation of the

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constitutive androstane receptor induces the expression of xenobiotic transporters and detoxifying enzymes, thereby protecting $CD4^+$ T effector cells in the lamina propria from harmful hydrophobic bile acids. Constitutive androstane receptor activation by bile acids also promotes the expression of the anti-inflammatory cytokine IL-10.[142]

Overall, these studies highlight the crucial role of microbiome-derived bile acids as signaling molecules, particularly in the regulation of adaptive immunity. Whether this also facilitates intestine-liver communication in regulating liver function and/or disease progression remains to be determined. It is worth noting that local activation of effector T cells has been shown to reduce the production of harmful bile acids in hepatocytes,[36] emphasizing the reciprocal interaction between immune responses and metabolism.

THE IMMUNE DYSREGULATION AND THE ULTIMATE DAMAGE TO THE BILIARY EPITHELIUM

Damage to the intrahepatic biliary epithelium in PBC is perpetrated by an orchestrated activation of a dysregulated immune system. The current paradigm is that the ultimate damage to the biliary epithelium in early PBC is driven by the T_H1 immune response, whereas in the late stage, the damage is sustained by T_H17.[115] However, both innate and adaptive immunity have a role in the genesis of inflammation, and likely, neither would suffice to cause the damage without the other's contribution.

Innate immunity is thought to be a key driver of the tolerance breakdown. The homeostatic balance in the liver of patients with PBC might be broken by the hyperresponsiveness of monocytes and macrophages to the inflammatory stimuli. The number of nonclassical monocytes (ie, $CD14^{high}$ and $CD16^{low}$) is increased in PBC patients, with a direct correlation between the number of these cell subsets and liver injury severity (defined as higher liver function tests). In fact, in vitro data demonstrated an increased release of inflammatory cytokines, such as IL-1, IL-6, IL-18, IL-12, and TNF-α, by monocytes in patients with PBC, compared with disease and healthy controls, on TLR stimulation.[79] Nonclassical monocytes are a major source of IL-8, a cytokine found increased in patients with PBC and capable of activating macrophages, which are themselves secretors of this cytokine, starting a vicious cycle.[143,144] We have already mentioned the hyperresponsiveness of macrophages to PDC-E2 found in apoptotic blebs. Macrophages from PBC have a pronounced M1 polarisation and, when exposed to the antigen exposed on apoptotic blebs, release a high level of IL-12 and upregulate TNF-related apoptosis-inducing ligand.[145,146] The infiltration of monocytes and macrophages is likely to be mediated by activated BECs; they are capable of releasing chemokines like CCL2 and CX3CL1, attracting monocytes and macrophages expressing CCR2 and CX3CR1 receptors respectively. Experimental models using 2-octynoic acid-bovine serum albumin have shown that disrupting these chemokine pathways can reduce liver inflammation and fibrosis.[107]

An intriguing player in the biliary damage in PBC is the NK cells. These are a subset of effector lymphocyte of the innate immune system which have, however, been demonstrated to have immunological memory, functioning effectively halfway through innate and adaptive immunity.[147–149] They account for approximately 30% of liver lymphocytes and have exhibited denser localization in portal tracts of PBC patients compared with that of non-PBC diseased and healthy controls. The liver homing of NK cells in PBC is likely mediated by the liver homing marker, CXCR6. Hydes and colleagues have demonstrated an upregulation of this marker in NK cells isolated from the peripheral blood of patients with PBC on exposure to low levels of IL-12, showing once more the centrality of this cytokine in PBC pathogenesis. The authors also demonstrated constitutive activation of NKs in PBC, participating as proinflammatory players when migrated to the liver.[150] The NK/BEC ratio in vitro proved to be a factor in determining the activity of NK cells against BECs. When the ratio was lower (acting as a model of early disease), NKs secreted IFN-γ, which upregulated MHC I and II expression on the BEC surface. While this discourages NK-mediate cytotoxicity, it makes BECS more susceptible to autoreactive cytotoxic T-cell clones, arguably further contributing to the tolerance breakdown. On the other end, when this ratio was high, it was associated with a pronounced NK cell–mediated BEC injury, autoantigen release, and perpetuation of the autoimmune process.[151]

The interest in MAIT cells as a player in cholestatic liver disease is relatively recent. As mentioned earlier, they have been named as a “biliary firewall” because they reside around the bile ducts, acting as a microbial sieve.[127] They are abundant in peripheral organs, and in the liver, yet increased liver infiltration with a parallel reduction in peripheral populations has been described in patients with PBC. Furthermore, an aberrant IL-17 secretion by MAIT cells on chronic IL-12 stimulation has been described by Bottcher and colleagues, which might play a role in the fibrogenesis by HSCs.[152,153]

The contribution of the adaptive immune system to PBC is easily exemplified by the rich infiltrate of T lymphocytes around the afflicted bile ducts. Data accumulated over time on the antigen specificity of such cells, which are 10 times more common in the portal tracts compared with peripheral blood, elude to them being the spark to sustain the bystander inflammation and the biliary damage.[7–9,154] Kita and

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colleagues, alongside characterizing the main epitope within PDC-E2, demonstrated also that autoantigen immunocomplexes could be presented on DCs through cross-presentation. The effectiveness of this interaction for presentation was found also relatively enhanced.[7,8] The well-orchestrated immune process among innate and adaptive immunity overall causes an increase of chemokine in the portal tract of PBC patients, such as CXCL10, CXCL9, and CX3CL1, thereby recruiting T cells expressing their cognate receptor.[107,155,156]

Throughout this review, the role of IL-12 has been mentioned several times. This cytokine, likely secreted by innate immune cells like macrophages and even BECs themselves, polarises $CD4^+$ T cells toward T_H1 on the antigen presentation. Besides the convincing results of GWAS showing several risk loci correlating with the IL-12 pathway,[40,157] other experimental evidence on the T_H1 role comes from animal models. We mentioned earlier how chronic exposure to IFN-γ, obtained through the deletion of 162 nt AU-rich in the untranslated region of the IFN gene, causes autoimmune cholangitis in ARE-$Del^{-/-}$ mice used as a model of PBC. These mice develop AMA at the age of 8–10 weeks, and liver injury with a female preponderance at 20 weeks. They ultimately develop an autoimmune cholangitis associated with granulomas. Of note, liver damage can be transferred to B6/$RAG1^{-/-}$ mice through adoptive transfer of $CD4^+$ T cells from ARE-$Del^{-/-}$ mice.[46,158,159]

Along with T_H1 cells, activated BECs secrete also T_H17-polarising cytokines such as IL-6, IL-1β, and IL-23.[160] Accordingly, T_H17 cells accumulate around the bile ducts. Further proof of the role of this pathway in PBC is the increased levels of IL-17 in the serum of patients with PBC and, in late-stage disease, T_H17 cells within their liver.[161,162] Furthermore, the immune-mediated damage and AMA levels are reduced in some PBC murine models after knocking out IL-17A.[163] However, different results can be obtained using IL-2Rα$^{-/-}$ mice, in which the autoimmune cholangitis gets worse after knocking out IL-17A, suggesting a potential protective effect of this cytokine in this setting rather than pro-inflammatory.[164] These data were confirmed by Chan and colleagues using a different model, 2-Octynoic acid-BSA-immunized mice, in which they alternately administered IL17-A, IL17-F, or IL-21. Surprisingly, neither the administration of IL-17A nor IL-17F affected inflammation or fibrosis. In fact, the authors showed a reduced level of IFN-γ-secreting T_H1 cells in mice treated with IL-17A. Instead, they described a marked effect of IL-21 in worsening the autoimmune cholangitis and promoting fibrosis.[165]

In the last few years, the PBC literature landscape has been quite dense with interest around $CD8^+$ T cells and their cytotoxic effect on biliary epithelium. Historically, Gershwin and colleagues have provided compelling data demonstrating the key role of $CD8^+$ T cells in PBC. They used dnTGFβRII murine model to adoptively transfer $CD8^+$ T cells to RAG1 knockout mice and subsequently induced PBC-like autoimmune cholangitis, demonstrating a dense infiltrate of terminally differentiated $CD8^+$ T cells.[166] Similar results were found by Yang and colleagues, who used nonobese diabetic c3c4 mice as donors of either $CD8^+$ cells alone or $CD8^+$ and $CD4^+$ cells for adoptive transfer to NOD SCID mice. The autoimmune cholangitis could be transferred by $CD8^+$ T cells alone, while type 1 diabetes systems needed the transfer of both $CD8^+$ and $CD4^+$ T cells.[167,168]

Human data provides further characterization for the phenotype of $CD8^+$ T-cell populations involved in the PBC pathogenesis. Chronic antigenic stimulation within the liver of patients with PBC causes the infiltration of terminally differentiated $CD45RO^{high}CD57^+CD8^{high}$ T cells.[169,170] The infiltrating cells become a source of chemokines (ie, CX3CL1,) beginning and perpetuating a vicious cycle, attracting more T cells from the peripheral blood. Li et al provided further data pointing toward $CD8^+$ T cells as the perpetrator of the biliary damage; they found a florid infiltrate of terminally differentiated $CD8^+$ T cells expressing killer cell lectin-like receptor $G1^+$ ($KLRG1^+$), Granzyme B, and Perforin in the portal tract of patients with PBC with higher levels of ALP and an increased risk of requiring liver transplantation.[168]

Huang and colleagues from Xiong lab described an expanded PDC-E2-specific, $CD103^+$ resident memory T cell (T_{RM}) population within the liver as the main autoreactive and cytotoxic cells in PBC livers. They speculated that the organ specificity and chronic fashion of PBC could be justified by the longevity of these cells and their inability to egress from the liver environment. Interestingly, they found nucleoside diphosphate X hydrolase 1, a nucleotide pool sanitizing enzyme, crucial for improving tolerance to oxidative stress, further justifying both the longevity of this cell population and the likelihood of their role in autoreactivity. To sustain this hypothesis, the authors tried to knock down or pharmacologically block nucleoside diphosphate X hydrolase 1, which showed a significant reduction of portal inflammation. Furthermore, UDCA treatment reduced the number of T_{RM} cells, suggesting also a prognostic role for these cells.[171]

Our lab recently demonstrated the existence of a subset of E-cadherin–expressing $CD8^+$ T cells that also possessed markers of tissue-resident memory cells ($T_{RM;}$ $CD69^+$ $CD103^+$ cells). These cells were capable of invading BECs through a process we term AVentosis, the frequency of which we showed correlated with the expression of E-cadherin by these T cells. Importantly, we demonstrated that $CD8^+$ T cells derived from patients with PBC expressed more E-cadherin on TCR stimulation compared to controls. Additionally, our data showed an increased cytotoxicity capacity of

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this cell subset and a correlation between hepatic cytolytic markers and the frequency of T_{RM} cells.[94] Zhang and colleagues also correlated $CD8^+$ T cells emperipolesis within BECs with apoptotic markers within them, suggesting that AVentosis is likely another mechanism of biliary damage.[95]

To strengthen the evidence that the biliary inflammation is ultimately executed by T_{RM} cells, Zhu and colleagues recently identified highly activated and cytotoxic $CD8^+$ T_{RM} cells in the liver of $Il12b^{-/-}Il2ra^{-/-}$ murine model. These cells upregulated several immune checkpoint molecules, including PD-1. The authors showed in the same model how knocking down *Cd8a* or treating the mice with anti-CD8α prevented or reduced the biliary damage. They developed a chimeric antigen receptor (CAR) targeting PD-1 expressing $CD8^+$ T_{RM} cells; using PD-1 targeting CAR-T cells, they demonstrated both a selective and efficacious approach in treating autoimmune cholangitis.[172]

Altogether, these studies suggested that damage to the BECs is ultimately perpetrated by $CD8^+$ T_{RM} cells. The latest evidence has further defined this cytotoxic population, characterized by markers such as nucleoside diphosphate X hydrolase 1, E-cadherin, and PD-1. This offers new outlooks for developing anti-inflammatory treatments to offer patients with PBC.

CONCLUSIONS: OLD AND NOVEL POTENTIAL THERAPEUTIC STRATEGIES IN PBC

This review explored the basis of the immunological architecture of PBC. We have presented the autoimmune hypothesis, which describes the aberrant states of cells and immune pathways found in patients with PBC, which eventually converge to drive the disease's pathogenesis. This model is well substantiated by data and can be recapitulated in animal models. The efforts in dissecting the disease pathogenesis share an ultimate purpose which is to develop a targeted treatment. However, despite extensive research and numerous attempts over the past 4 decades to identify effective immune-modulating treatments, significant challenges remain. Prototype immune modulators, such as corticosteroids, have proven ineffective in PBC, even when used as adjunctive therapies.[14,173,174] Further attempts with different classes of drugs, like colchicine and penicillamine,[175,176] antivirals such as lamivudine,[177] as well as immunosuppressants like azathioprine and methotrexate, have been tested.[11,178,179] However, these treatments have generally demonstrated only marginal efficacy, or have been associated with potential harm, leading to their exclusion from current treatment recommendations.

More recent attempts with targeted immunological treatment have still failed in proving meaningful clinical effects. For instance, rituximab, an anti-CD20 monoclonal antibody, showed some promise by reducing ALP levels in a small cohort of patients, but overall clinical efficacy remained limited.[180] High expectations were put on Ustekinumab, which targets the IL-12 and IL-23 pathways, based on experimental and genetic data supplementing a strong biological rationale. However, it did not achieve significant improvements in ALP levels in larger patient groups, despite some biochemical indications of pathway modulation.[181,182] These outcomes highlight the paradoxical nature of PBC, where conventional and even specific immunosuppressive strategies fail to effectively control disease. In the advanced stages of PBC, liver transplantation remains the only definitive treatment option, offering substantial improvements in graft and patient survival rates. Nonetheless, recurrence of PBC post-transplantation remains a frequent concern.[183]

The currently used treatments for PBC action through bile acid metabolism and the secretory machinery of BECs. These molecules, UDCA, FXR agonists like obethicolic acid, and PPAR agonists, also have an effect on immune pathways. It would likely be helpful for the general understanding of PBC pathogenesis to fully detail the immune effects of these molecules. For instance, UDCA possesses multiple immune-modulating properties. It decreases the expression of MHC class I and II proteins on BECs, thereby reducing antigen presentation and the activation of autoreactive T cells.[184] This may help restore immune tolerance and break the inflammatory cascade driven by cytotoxic $CD8^+$ T cells, T_H1 cells, and macrophages. Additionally, UDCA exerts anti-apoptotic effects where are mediated through the modulation of survival signaling pathways, such as NF-κB, AKT, MAPK, and PI3K.[185] Such effects not only prevent biliary damage but it also interrupts antigen spreading and reduces inflammatory triggers. Additionally, UDCA restores natural killer T-cell activity by reducing prostaglandin E_2 production, fostering a balanced immune environment and preventing the shift toward a T_H17-dominated response that promotes fibrosis.[186]

In cases where UDCA treatment is inadequate, second-line therapies targeting bile acid metabolism, such as obeticholic acid and FXR agonists, are used. These therapies aim to further modulate bile acid synthesis and transport, enhance intestinal barrier function, and reduce hepatic inflammation. However, even for FXR agonists, there are several well-described effects on the immune system. McMahan et al showed that the FXR and TGR5 agonism skewed monocytes to an anti-inflammatory phenotype in obese mice.[187] Moreover, FXR stimulation was shown to induce monocyte production of IL-10 in vitro. Additional experimental models have

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demonstrated that FXR agonists can decrease the recruitment of natural killer (NK) cells and the production of IFN-γ, thereby mitigating immune-mediated liver damage and bacterial translocation from the gut.[188] Also, OCA shows an effect in apoptosis reduction on NF-κB activation.

PPAR-α and PPAR-δ agonists have also shown promise in inhibiting profibrotic pathways and reducing inflammation. PPARs are nuclear receptors that regulate gene expression involved in lipid metabolism, inflammation, and immune responses. Activation of PPAR-α and PPAR-δ leads to the suppression of proinflammatory cytokine production, inhibition of NF-κB signaling, and modulation of immune cell differentiation and function. Specifically, PPAR agonists regulate T-cell responses by promoting the differentiation of Treg cells while inhibiting the proliferation and function of proinflammatory T_H1 and T_H17 cells. This shift enhances immune tolerance and reduces autoimmune-mediated damage to cholangiocytes. Additionally, PPAR agonists induce an anti-inflammatory phenotype in macrophages, reducing the secretion of proinflammatory cytokines such as TNF-α and IL-6. This inhibits the activation of HSCs, which are central to fibrosis development. By regulating the expression of genes involved in bile acid transport and synthesis, PPAR agonists help maintain bile acid balance, thereby reducing hepatobiliary stress and subsequent immune activation.[189,190]

The paradigm of treatment is shifting in autoimmunity from treating to curing. The recent evidence of using CAR-T-cell approaches that target B cells in complex autoimmune conditions is certainly gaining attention and pushing the field forward.[191] In the case of the liver, remodeling the liver microenvironment, changing the cell composition, and re-establishing immune homeostasis should be set as the treatment goal. Furthermore, a more targeted approach in this instance relies on a deep knowledge of the self-antigen (PDC-E2), a unique opportunity offered by PBC. The excitement surrounding new technologies in cellular engineering and therapy may drive this shift from chronic treatment to a possible cure. The recent data on CAR technology targeting PD-1$^+$ T_{RM} cells may open new treatment venues, although it remains to be seen how these results translate to humans.

Increasing the number or reprogramming of Treg cells is another therapy venue currently being pursued in several autoimmune conditions. These treatment approaches are several, and none of them are without challenges. In situ expansion of Tregs can be obtained using low doses of IL-2, selectively targeting Tregs that express the high-affinity IL-2Rα (CD25) and avoiding the proliferation of the cytotoxic population. This approach has been tested in several autoimmune diseases, including lupus and diabetes. The use of low-dose IL-2 significantly boosted the number of Tregs but with a significant increase also on NK and CD8$^+$ T cells.[192]

We tested the ex vivo expansion of Tregs from patients with autoimmune hepatitis and the reinfusion of the cell product. This early phase trial proved that the treatment was very well tolerated. We also showed that the Tregs after reinfusion localised mainly within the liver, most likely due to the homing to the inflamed organ.[69] A similar approach is currently under investigation in our lab for PBC.

The collateral effect of inducing a broad tolerance toward dangerous antigens can be overcome by inducing or transferring antigen-specific Treg cells. However, moving from a polyclonal Treg therapy to an antigen-specific approach in humans remains incredibly challenging. The expansion of autoreactive clones from the periphery poses two issues; first, the identification of the autoreactive clones relies on engineered tetramers, which should target the epitope of interest. The second is the isolation and the subsequent expansion of the cell population, which could require a long time to reach a therapeutic concentration. Alternatively, engineering the TCR to generate antigen-specific clones is certainly an emerging approach.[193] Sakaguchi's group proposed an epigenetic reprogramming of CD4$^+$ T cells to induce stable and functioning Treg cells by inhibiting cyclin-dependent kinase 8 and 19. This approach allows for the selection of CD4$^+$ T memory cells and conversion of them into induced Tregs by promoting the expression of FOXP3.[194]

Over the past few decades, and especially in the last 10 years, the clinical management of PBC has advanced significantly. We now have several options as second-line treatments, and we have the ability to identify complex cases early using stratification tools. However, the underlying causes of PBC remain elusive. The variety of experimental findings to date has not yet led to a comprehensive understanding of the disease's pathogenesis. Immunologically, PBC stands out as a unique model for studying autoimmunity. This is due to its well-defined disease epitopes, slow disease progression, and relatively consistent phenotype among patients. Moving forward, ongoing research is crucial to decipher the complexities of PBC to develop more targeted therapies and even reestablish the tolerance toward the antigen in these patients.

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CONFLICTS OF INTEREST

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REFERENCES

1. Lleo A, Wang GQ, Gershwin ME, Hirschfield GM. Primary biliary cholangitis. Lancet. 2020;396:1915–26.
2. Walker JG, Doniach D, Roitt IM, Sherlock S. Serological tests in diagnosis of primary biliary cirrhosis. Lancet. 1965;1:827–31.
3. Berg PA, Doniach D, Roitt IM. Mitochondrial antibodies in primary biliary cirrhosis. I. Localization of the antigen to mitochondrial membranes. J Exp Med. 1967;126:277–90.
4. Berg PA, Klein R. Antimitochondrial antibodies in primary biliary cirrhosis and other disorders: Definition and clinical relevance. Dig Dis. 1992;10:85–101.
5. Gershwin ME, Mackay IR, Sturgess A, Coppel RL. Identification and specificity of a cDNA encoding the 70 kd mitochondrial antigen recognized in primary biliary cirrhosis. J Immunol. 1987;138:3525–31.
6. Frazer IH, Mackay IR, Jordan TW, Whittingham S, Marzuki S. Reactivity of anti-mitochondrial autoantibodies in primary biliary cirrhosis: Definition of two novel mitochondrial polypeptide autoantigens. J Immunol. 1985;135:1739–45.
7. Kita H, Matsumura S, He XS, Ansari AA, Lian ZX, Van de Water J, et al. Quantitative and functional analysis of PDC-E2-specific autoreactive cytotoxic T lymphocytes in primary biliary cirrhosis. J Clin Invest. 2002;109:1231–40.
8. Kita H, Lian ZX, Van de Water J, He XS, Matsumura S, Kaplan M, et al. Identification of HLA-A2-restricted CD8(+) cytotoxic T cell responses in primary biliary cirrhosis: T cell activation is augmented by immune complexes cross-presented by dendritic cells. J Exp Med. 2002;195:113–23.
9. Shimoda S, Van de Water J, Ansari A, Nakamura M, Ishibashi H, Coppel RL, et al. Identification and precursor frequency analysis of a common T cell epitope motif in mitochondrial autoantigens in primary biliary cirrhosis. J Clin Invest. 1998;102:1831–40.
10. Biewenga M, Heidt S, Vergunst M, Marijnissen CMJ, de Man RA, van der Eijk AA, et al. B-cell activating factor and IL-21 levels predict treatment response in autoimmune hepatitis. JHEP Rep. 2022;4:100460.
11. Combes B, Emerson SS, Flye NL, Munoz SJ, Luketic VA, Mayo MJ, et al. Methotrexate (MTX) plus ursodeoxycholic acid (UDCA) in the treatment of primary biliary cirrhosis. Hepatology (Baltimore, Md). 2005;42:1184–93.
12. Rautiainen H, Kärkkäinen P, Karvonen AL, Nurmi H, Pikkarainen P, Nuutinen H, et al. Budesonide combined with UDCA to improve liver histology in primary biliary cirrhosis: A three-year randomized trial. Hepatology (Baltimore, Md). 2005;41:747–52.
13. Jayant AT, Angulo P, Keach JC, Petz JL, Jorgensen RA, Lindor KD. Mycophenolate mofetil for the treatment of primary biliary cirrhosis in patients with an incomplete response to ursodeoxycholic acid. J Clin Gastroenterol. 2005;39:168–71.
14. Leuschner M, Maier KP, Schlichting J, Strahl S, Herrmann G, Dahm HH, et al. Oral budesonide and ursodeoxycholic acid for treatment of primary biliary cirrhosis: Results of a prospective double-blind trial. Gastroenterology. 1999;117:918–25; pmid = 10500075.
15. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology. 2006;130:715–20.
16. Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology (Baltimore, Md). 2000;32:1196–9.
17. Degott C, Zafrani ES, Callard P, Balkau B, Poupon RE, Poupon R. Histopathological study of primary biliary cirrhosis and the effect of ursodeoxycholic acid treatment on histology progression. Hepatology (Baltimore, Md). 1999;29:1007–12.
18. Angulo P, Batts KP, Therneau TM, Jorgensen RA, Dickson RE, Lindor KD. Long-term ursodeoxycholic acid delays histological progression in primary biliary cirrhosis. Hepatology (Baltimore, Md). 1999;29:644–7.
19. Beuers U, Spengler U, Kruis W, Aydemir ü, Wiebecke B, Heldwein W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: A placebo-controlled trial. Hepatology. 1992;16:707–14.
20. Beuers U, Hohenester S, de Buy Wenniger LJM, Kremer AE, Jansen PLM, Elferink RPJO. The biliary HCO(3)(-) umbrella: A unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. Hepatology (Baltimore, Md). 2010;52:1489–96.
21. Banales JM, Sáez E, Úriz M, Sarvide S, Urribarri AD, Splinter P, et al. Up-regulation of microRNA 506 leads to decreased Cl-/HCO3- anion exchanger 2 expression in biliary epithelium of patients with primary biliary cirrhosis. Hepatology. 2012;56:687–97.
22. Hohenester S, de Buy Wenniger LM, Paulusma CC, van Vliet SJ, Jefferson DM, Oude Elferink RP, et al. A biliary HCO3-umbrella constitutes a protective mechanism against bile acid-induced injury in human cholangiocytes. Hepatology (Baltimore, Md). 2012;55:173–83.
23. Chang JC, Go S, de Waart DR, Munoz-Garrido P, Beuers U, Paulusma CC, et al. Soluble adenylyl cyclase regulates bile salt-induced apoptosis in human cholangiocytes. Hepatology. 2016;64:522–34.
24. Erice O, Munoz-Garrido P, Vaquero J, Perugorria MJ, Fernandez-Barrena MG, Saez E, et al. MicroRNA-506 promotes primary biliary cholangitis-like features in cholangiocytes and immune activation. Hepatology (Baltimore, Md). 2018;67:1420–40.
25. Rodrigues PM, Perugorria MJ, Santos-Laso A, Bujanda L, Beuers U, Banales JM. Primary biliary cholangitis: A tale of epigenetically-induced secretory failure? J Hepatol. 2018;69:1371–83.
26. Uriz M, Saez E, Prieto J, Medina JF, Banales JM. Ursodeoxycholic acid is conjugated with taurine to promote secretin-stimulated biliary hydrocholeresis in the normal rat. PloS One. 2011;6:e28717.
27. Salas JT, Banales JM, Sarvide S, Recalde S, Ferrer A, Uriarte I, et al. Ae2a,b-deficient mice develop antimitochondrial antibodies and other features resembling primary biliary cirrhosis. Gastroenterology. 2008;134:1482–93.
28. Banales JM, Arenas F, Rodríguez-Ortigosa CM, Sáez E, Uriarte I, Doctor BR, et al. Bicarbonate-rich choleresis induced by secretin in normal rat is taurocholate-dependent and involves AE2 anion exchanger. Hepatology. 2006;43:266–75.

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29. Prieto J, García N, Martí-Climent JM, Peñuelas I, Richter JA, Medina JF. Assessment of biliary bicarbonate secretion in humans by positron emission tomography. Gastroenterology. 1999;117:167–72.
30. Medina JF, Martinez A, Vazquez JJ, Prieto J. Decreased anion exchanger 2 immunoreactivity in the liver of patients with primary biliary cirrhosis. Hepatology (Baltimore, Md). 1997;25: 12–7.
31. Selmi C, Mayo MJ, Bach N, Ishibashi H, Invernizzi P, Gish RG, et al. Primary biliary cirrhosis in monozygotic and dizygotic twins: Genetics, epigenetics, and environment. Gastroenterology. 2004;127:485–92.
32. Jones DE, Watt FE, Metcalf JV, Bassendine MF, James OF. Familial primary biliary cirrhosis reassessed: A geographically-based population study. Journal of hepatology. 1999;30:402–7.
33. Gulamhusein AF, Lazaridis KN. Primary biliary cholangitis, DNA, and beyond: The relative contribution of genes. Hepatology. 2018;68:19–21.
34. Lazaridis KN, Juran BD, Boe GM, Slusser JP, de Andrade M, Homburger HA, et al. Increased prevalence of antimitochondrial antibodies in first-degree relatives of patients with primary biliary cirrhosis. Hepatology. 2007;46:785–92.
35. Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet. 2007;39:857–64.
36. Gerussi A, Carbone M, Corpechot C, Schramm C, Asselta R, Invernizzi P. The genetic architecture of primary biliary cholangitis. Eur J Med Genet. 2021;64:104292.
37. Nakamura M, Nishida N, Kawashima M, Aiba Y, Tanaka A, Yasunami M, et al. Genome-wide association study identifies TNFSF15 and POU2AF1 as susceptibility loci for primary biliary cirrhosis in the Japanese population. American journal of human genetics. 2012;91:721–8.
38. Mells GF, Floyd JAB, Morley KI, Cordell HJ, Franklin CS, Shin SY, et al. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. Nat Genet. 2011; 43:329–32.
39. Cordell HJ, Fryett JJ, Ueno K, Darlay R, Aiba Y, Hitomi Y, et al. An international genome-wide meta-analysis of primary biliary cholangitis: Novel risk loci and candidate drugs. J Hepatol. 2021;75:572–81.
40. Hirschfield GM, Liu X, Xu C, Lu Y, Xie G, Lu Y, et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. N Engl J Med. 2009;360:2544–55.
41. Hirschfield GM, Liu X, Han Y, Gorlov IP, Lu Y, Xu C, et al. Variants at IRF5-TNPO3, 17q12-21 and MMEL1 are associated with primary biliary cirrhosis. Nat Genet. 2010;42:655–7.
42. Liu X, Invernizzi P, Lu Y, Kosoy R, Lu Y, Bianchi I, et al. Genome-wide meta-analyses identify three loci associated with primary biliary cirrhosis. Nat Genet. 2010;42:658–60.
43. Ronca V, Carbone M, Bernuzzi F, Malinverno F, Mousa HS, Gershwin ME, et al. From pathogenesis to novel therapies in the treatment of primary biliary cholangitis. Expert Review of Clinical Immunology. 2017;13:1121–31.
44. Carbone M, Ronca V, Bruno S, Invernizzi P, Mells GF. Toward precision medicine in primary biliary cholangitis. Dig Liver Dis. 2016;48:843–50.
45. Farh KKH, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature. 2015;518:337–43.
46. Bae HR, Leung PSC, Tsuneyama K, Valencia JC, Hodge DL, Kim S, et al. Chronic expression of interferon-gamma leads to murine autoimmune cholangitis with a female predominance. Hepatology (Baltimore, Md). 2016;64:1189–201.
47. Yoshida K, Yang GX, Zhang W, Tsuda M, Tsuneyama K, Moritoki Y, et al. Deletion of interleukin-12p40 suppresses autoimmune cholangitis in dominant negative transforming growth factor beta receptor type II mice. Hepatology (Baltimore, Md). 2009;50:1494–500.
48. Liu JZ, Almarri MA, Gaffney DJ, Mells GF, Jostins L, Cordell HJ, et al. Dense fine-mapping study identifies new susceptibility loci for primary biliary cirrhosis. Nat Genet. 2012;44:1137–41.
49. Juran BD, Hirschfield GM, Invernizzi P, Atkinson EJ, Li Y, Xie G, et al. Immunochip analyses identify a novel risk locus for primary biliary cirrhosis at 13q14, multiple independent associations at four established risk loci and epistasis between 1p31 and 7q32 risk variants. Hum Mol Genet. 2012;21:5209–21.
50. Yang F, Yang Y, Wang Q, Wang Z, Miao Q, Xiao X, et al. The risk predictive values of UK-PBC and GLOBE scoring system in Chinese patients with primary biliary cholangitis: The additional effect of anti-gp210. Aliment Pharmacol Ther. 2017; 45:733–43.
51. Ronca V, Mancuso C, Milani C, Carbone M, Oo YH, Invernizzi P. Immune system and cholangiocytes: A puzzling affair in primary biliary cholangitis. J Leukoc Biol. 2020;108:659–71.
52. Carbone M, Milani C, Gerussi A, Ronca V, Cristoferi L, Invernizzi P. Primary biliary cholangitis: A multifaceted pathogenesis with potential therapeutic targets. J Hepatol. 2020;73:965–6.
53. Warner S, Rajanayagam J, Russell E, Lloyd C, Ferguson J, Kelly DA, et al. Biliary disease progression in childhood onset autoimmune liver disease: A 30-year follow-up into adulthood. JHEP Rep. 2024;6:100901.
54. Osei-Bordom D, Bozward AG, Oo YH. The hepatic microenvironment and regulatory T cells. Cell Immunol. 2020;357: 104195.
55. Jeffery HC, Hunter S, Humphreys EH, Bhogal R, Wawman RE, Birtwistle J, et al. Bidirectional cross-talk between iliary epithelium and Th17 cells promotes local Th17 expansion and bile duct proliferation in biliary liver diseases. J Immunol. 2019; 203:1151–9.
56. Oo YH, Banz V, Kavanagh D, Liaskou E, Withers DR, Humphreys E, et al. CXCR3-dependent recruitment and CCR6-mediated positioning of Th-17 cells in the inflamed liver. J Hepatol. 2012;57:1044–51.
57. Fumi KV, Joe W, Timothy RC. An increased risk of urinary tract infection precedes development of primary biliary cirrhosis. BMC gastroenterology. 2011;11:95.
58. Selmi C, Balkwill DL, Invernizzi P, Ansari AA, Coppel RL, Podda M, et al. Patients with primary biliary cirrhosis react against a ubiquitous xenobiotic-metabolizing bacterium. Hepatology. 2003;38:1250–7.
59. Tanaka A, Leung PSC, Gershwin ME. Pathogen infections and primary biliary cholangitis. Clinical and experimental immunology. 2019;195:25–34.
60. Corpechot C, Chrétien Y, Chazouillères O, Poupon R. Demographic, lifestyle, medical and familial factors associated with primary biliary cirrhosis. J Hepatol. 2010;53:162–9.
61. Dimitrios PB, Harold B, Diego V, Andrew KB. The role of E. coli infection in the pathogenesis of primary biliary cirrhosis. Dis Markers. 2010;29:301–11.
62. Palermo JJ. W1846 recurrent urinary tract infection in mice results in immune-mediated cholangiopathy similar to human primary biliary cirrhosis. Gastroenterology. 2008;134:A-837.
63. Gershwin EM, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, et al. Risk factors and comorbidities in primary biliary cirrhosis: A controlled interview-based study of 1032 patients. Hepatology (Baltimore, Md). 2005;42:1194–202.
64. Butler PH-MJBH, Burroughs AK. Detection of M2 antibodies in patients with recurrent urinary tract infection using an ELISA and purified PBC specific antigens. Evidence for a molecular mimicry mechanism in the pathogenesis of primary biliary cirrhosis? Biochem Mol Biol Int. 1995;35:473.
65. Hamlyn AN, Macklon AF, James O. Primary biliary cirrhosis: Geographical clustering and symptomatic onset seasonality. Gut. 1983;24:940–5.

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66. Amano K, Leung PSC, Rieger R, Quan C, Wang X, Marik J, et al. Chemical xenobiotics and mitochondrial autoantigens in primary biliary cirrhosis: Identification of antibodies against a common environmental, cosmetic, and food additive, 2-octynoic acid. J Immunol. 2005;174:5874–83.
67. Wakabayashi K, Lian ZX, Leung PSC, Moritoki Y, Tsuneyama K, Kurth MJ, et al. Loss of tolerance in C57BL/6 mice to the autoantigen E2 subunit of pyruvate dehydrogenase by a xenobiotic with ensuing biliary ductular disease. Hepatology. 2008;48:531–40.
68. Lleo A, Liao J, Invernizzi P, Zhao M, Bernuzzi F, Ma L, et al. Immunoglobulin M levels inversely correlate with CD40 ligand promoter methylation in patients with primary biliary cirrhosis. Hepatology. 2012;55:153–60.
69. Oo YH, Ackrill S, Cole R, Jenkins L, Anderson P, Jeffery HC, et al. Liver homing of clinical grade Tregs after therapeutic infusion in patients with autoimmune hepatitis. JHEP Rep. 2019;1:286–96.
70. Oo YH, Weston CJ, Lalor PF, Curbishley SM, Withers DR, Reynolds GM, et al. Distinct Roles for CCR4 and CXCR3 in the Recruitment and Positioning of Regulatory T Cells in the Inflamed Human Liver. J Immunol. 2010;184: 2886–98.
71. Goddard S, Williams A, Morland C, Qin S, Gladue R, Hubscher SG, et al. Differential expression of chemokines and chemokine receptors shapes the inflammatory response in rejecting human liver transplants. Transplantation. 2001;72: 1957–67.
72. Lleo A, Zhang W, Zhao M, Tan Y, Bernuzzi F, Zhu B, et al. DNA methylation profiling of the X chromosome reveals an aberrant demethylation on CXCR3 promoter in primary biliary cirrhosis. Clin Epigenetics. 2015;7:61.
73. Asselta R, Paraboschi EM, Gerussi A, Cordell HJ, Mells GF, Sandford RN, et al. X chromosome contribution to the genetic architecture of primary biliary cholangitis. Gastroenterology. 2021;160:2483–495 e2426.
74. Gerussi A, Cristoferi L, Carbone M, Asselta R, Invernizzi P. The immunobiology of female predominance in primary biliary cholangitis. J Autoimmun. 2018;95:124–32.
75. Bartel DP. Metazoan microRNAs. Cell. 2018;173:20–51.
76. Gerussi A, Paraboschi EM, Cappadona C, Caime C, Binatti E, Cristoferi L, et al. The role of epigenetics in primary biliary cholangitis. Int J Mol Sci. 2022;23:4873.
77. Ando Y, Yang GX, Kenny TP, Kawata K, Zhang W, Huang W, et al. Overexpression of microRNA-21 is associated with elevated pro-inflammatory cytokines in dominant-negative TGF-β receptor type II mouse. J Autoimmun. 2013;41:111–9.
78. Li Y, Li Z, Chen R, Lian M, Wang H, Wei Y, et al. A regulatory variant at 19p13.3 is associated with primary biliary cholangitis risk and ARID3A expression. Nat Commun. 2023;14: 1732.
79. Mao TK, Lian ZX, Selmi C, Ichiki Y, Ashwood P, Ansari AA, et al. Altered monocyte responses to defined TLR ligands in patients with primary biliary cirrhosis. Hepatology (Baltimore, Md). 2005;42:802–8.
80. Yan C, Koda S, Wu J, Zhang BB, Yu Q, Netea MG, et al. Roles of trained immunity in the pathogenesis of cholangiopathies: A therapeutic target. Hepatology (Baltimore, Md). 2020;72: 1838–50.
81. Oertelt S, Lian ZX, Cheng CM, Chuang YH, Padgett KA, He XS, et al. Anti-mitochondrial antibodies and primary biliary cirrhosis in TGF-beta receptor II dominant-negative mice. J Immunol. 2006;177:1655–60.
82. Wakabayashi K, Lian ZX, Moritoki Y, Lan RY, Tsuneyama K, Chuang YH, et al. IL-2 receptor alpha(-/-) mice and the development of primary biliary cirrhosis. Hepatology. 2006;44: 1240–9.
83. Zhang W, Sharma R, Ju ST, He XS, Tao Y, Tsuneyama K, et al. Deficiency in regulatory T cells results in development of antimitochondrial antibodies and autoimmune cholangitis. Hepatology. 2009;49:545–52.
84. Liaskou E, Patel SR, Webb G, Bagkou Dimakou D, Akiror S, Krishna M, et al. Increased sensitivity of Treg cells from patients with PBC to low dose IL-12 drives their differentiation into IFN-gamma secreting cells. J Autoimmun. 2018;94:143–55.
85. Tanaka H, Zhang W, Yang GX, Ando Y, Tomiyama T, Tsuneyama K, et al. Successful immunotherapy of autoimmune cholangitis by adoptive transfer of forkhead box protein 3(+) regulatory T cells. Clin Exp Immunol. 2014;178:253–61.
86. Lazaridis KN, Strazzabosco M, Larusso NF. The cholangiopathies: Disorders of biliary epithelia. Gastroenterology. 2004;127: 1565–77.
87. Strazzabosco M, Spirli C, Okolicsanyi L. Pathophysiology of the intrahepatic biliary epithelium. J Gastroenterol Hepatol. 2000; 15:244–53.
88. Koga H, Sakisaka S, Ohishi M, Sata M, Tanikawa K. Nuclear DNA fragmentation and expression of Bcl-2 in primary biliary cirrhosis. Hepatology. 1997;25:1077–84.
89. Takeda K, Kojima Y, Ikejima K, Harada K, Yamashina S, Okumura K, et al. Death receptor 5 mediated-apoptosis contributes to cholestatic liver disease. Proc Natl Acad Sci U S A. 2008;105:10895–900.
90. Salunga TL, Cui ZG, Shimoda S, Zheng HC, Nomoto K, Kondo T, et al. Oxidative stress-induced apoptosis of bile duct cells in primary biliary cirrhosis. J Autoimmun. 2007;29:78–86.
91. Lleo A, Selmi C, Invernizzi P, Podda M, Gershwin ME. The consequences of apoptosis in autoimmunity. J Autoimmun. 2008;31:257–62.
92. Davies SP, Reynolds GM, Stamataki Z. Clearance of apoptotic cells by tissue epithelia: A putative role for hepatocytes in liver efferocytosis. Front Immunol. 2018;9:44.
93. Allina J, Stanca CM, Garber J, Hu B, Sautes-Fridman C, Bach N, et al. Anti-CD16 autoantibodies and delayed phagocytosis of apoptotic cells in primary biliary cirrhosis. J Autoimmun. 2008; 30:238–45.
94. Davies SP, Ronca V, Wootton GE, Krajewska NM, Bozward AG, Fiancette R, et al. Expression of E-cadherin by CD8(+) T cells promotes their invasion into biliary epithelial cells. Nat Commun. 2024;15:853.
95. Zhao S, Li W, Fu N, Zhou G, Liu S, Jiang L, et al. Emperipolesis mediated by CD8 + T cells correlates with biliary epithelia cell injury in primary biliary cholangitis. J Cell Mol Med. 2020;24: 1268–75.
96. Concepcion AR, Lopez M, Ardura-Fabregat A, Medina JF. Role of AE2 for pHi regulation in biliary epithelial cells. Front Physiol. 2013;4:413.
97. Alvaro D, Cho WK, Mennone A, Boyer JL. Effect of secretion on intracellular pH regulation in isolated rat bile duct epithelial cells. J Clin Invest. 1993;92:1314–25.
98. Harada K, Isse K, Kamihira T, Shimoda S, Nakanuma Y. Th1 cytokine-induced downregulation of PPARgamma in human biliary cells relates to cholangitis in primary biliary cirrhosis. Hepatology. 2005;41:1329–38.
99. Chen XM, O'Hara SP, Nelson JB, Splinter PL, Small AJ, Tietz PS, et al. Multiple TLRs are expressed in human cholangiocytes and mediate host epithelial defense responses to Cryptosporidium parvum via activation of NF-kappaB. J Immunol. 2005;175:7447–56.
100. Takii Y, Nakamura M, Ito M, Yokoyama T, Komori A, Shimizu-Yoshida Y, et al. Enhanced expression of type I interferon and toll-like receptor-3 in primary biliary cirrhosis. Lab Invest. 2005; 85:908–20.
101. Wang AP, Migita K, Ito M, Takii Y, Daikoku M, Yokoyama T, et al. Hepatic expression of toll-like receptor 4 in primary biliary cirrhosis. J Autoimmun. 2005;25:85–91.

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102. Moritoki Y, Lian ZX, Wulff H, Yang GX, Chuang YH, Lan RY, et al. AMA production in primary biliary cirrhosis is promoted by the TLR9 ligand CpG and suppressed by potassium channel blockers. Hepatology (Baltimore, Md). 2007;45:314–22.
103. Nakanuma Y, Sasaki M, Harada K. Autophagy and senescence in fibrosing cholangiopathies. J Hepatol. 2015;62:934–45.
104. Sasaki M, Miyakoshi M, Sato Y, Nakanuma Y. Increased expression of mitochondrial proteins associated with autophagy in biliary epithelial lesions in primary biliary cirrhosis. Liver Int. 2013;33:312–20.
105. Sasaki M, Miyakoshi M, Sato Y, Nakanuma Y. Autophagy mediates the process of cellular senescence characterizing bile duct damages in primary biliary cirrhosis. Lab Invest. 2010;90: 835–43.
106. Sasaki M, Ikeda H, Haga H, Manabe T, Nakanuma Y. Frequent cellular senescence in small bile ducts in primary biliary cirrhosis: A possible role in bile duct loss. J Pathol. 2005;205: 451–9.
107. Sasaki M, Miyakoshi M, Sato Y, Nakanuma Y. Chemokine-chemokine receptor CCL2-CCR2 and CX3CL1-CX3CR1 axis may play a role in the aggravated inflammation in primary biliary cirrhosis. Dig Dis Sci. 2014;59:358–64.
108. Li X, Li Y, Xiao J, Wang H, Guo Y, Mao X, et al. Unique DUOX2 (+)ACE2(+) small cholangiocytes are pathogenic targets for primary biliary cholangitis. Nat Commun. 2023;14:29.
109. Ronca V, Wootton G, Milani C, Cain O. The immunological basis of liver allograft rejection. Frontiers in immunology. 2020; 11:2155.
110. Arii S, Imamura M. Physiological role of sinusoidal endothelial cells and Kupffer cells and their implication in the pathogenesis of liver injury. J Hepatobiliary Pancreat Surg. 2000;7:40–8.
111. Tiegs G, Lohse AW. Immune tolerance: What is unique about the liver. J Autoimmun. 2010;34:1–6.
112. Crispe IN. The liver as a lymphoid organ. Annu Rev Immunol. 2009;27:147–63.
113. Warren A, Le Couteur DG, Fraser R, Bowen DG, McCaughan GW, Bertolino P. T lymphocytes interact with hepatocytes through fenestrations in murine liver sinusoidal endothelial cells. Hepatology (Baltimore, Md). 2006;44:1182–90.
114. Odin JA, Huebert RC, Casciola-Rosen L, LaRusso NF, Rosen A. Bcl-2-dependent oxidation of pyruvate dehydrogenase-E2, a primary biliary cirrhosis autoantigen, during apoptosis. J Clin Invest. 2001;108:223–32.
115. Yang CY, Ma X, Tsuneyama K, Huang S, Takahashi T, Chalasani NP, et al. IL-12/Th1 and IL-23/Th17 biliary microenvironment in primary biliary cirrhosis: Implications for therapy. Hepatology. 2014;59:1944–53.
116. Lleo A, Bowlus CL, Yang GX, Invernizzi P, Podda M, Van de Water J, et al. Biliary apotopes and anti-mitochondrial antibodies activate innate immune responses in primary biliary cirrhosis. Hepatology. 2010;52:987–98.
117. You Z, Wang Q, Bian Z, Liu Y, Han X, Peng Y, et al. The immunopathology of liver granulomas in primary biliary cirrhosis. J Autoimmun. 2012;39:216–21.
118. Chu H, Li Y, Yang H, Liu Y, Zheng R, Zhang X, et al. Characterisation and clinical relevance of tertiary lymphoid structures in primary biliary cholangitis. Liver Int. 2024.
119. Pipi E, Nayar S, Gardner DH, Colafrancesco S, Smith C, Barone F. Tertiary lymphoid structures: Autoimmunity goes local. Frontiers in immunology. 2018;9:1952.
120. Krausgruber T, Redl A, Barreca D, Doberer K, Romanovskaia D, Dobnikar L, et al. Single-cell and spatial transcriptomics reveal aberrant lymphoid developmental programs driving granuloma formation. Immunity. 2023;56:289–306 e287.
121. Reuveni D, Assi S, Gore Y, Brazowski E, Leung PSC, Shalit T, et al. Conventional type 1 dendritic cells are essential for the development of primary biliary cholangitis. Liver Int. 2024;44: 2063–74.
122. Barbatis C, Woods J, Morton JA, Fleming KA, McMichael A, McGee JO. Immunohistochemical analysis of HLA (A, B, C) antigens in liver disease using a monoclonal antibody. Gut. 1981;22:985–91.
123. Leon MP, Bassendine MF, Wilson JL, Ali S, Thick M, Kirby JA. Immunogenicity of biliary epithelium: Investigation of antigen presentation to CD4+ T cells. Hepatology (Baltimore, Md). 1996;24:561–7.
124. Barnes BH, Tucker RM, Wehrmann F, Mack DG, Ueno Y, Mack CL. Cholangiocytes as immune modulators in rotavirus-induced murine biliary atresia. Liver International. 2009;29:1253–61.
125. Ronca V, Gerussi A, Collins P, Parente A, Oo YH, Invernizzi P. The liver as a central "hub" of the immune system: Pathophysiological implications. Physiol Rev. 2024.
126. Schrumpf E, Tan C, Karlsen TH, Sponheim J, Björkström NK, Sundnes O, et al. The biliary epithelium presents antigens to and activates natural killer T cells. Hepatology (Baltimore, Md). 2015;62:1249–59.
127. Jeffery HC, van Wilgenburg B, Kurioka A, Parekh K, Stirling K, Roberts S, et al. Biliary epithelium and liver B cells exposed to bacteria activate intrahepatic MAIT cells through MR1. J Hepatol. 2016;64:1118–27.
128. Straniero S, Laskar A, Savva C, Härdfeldt J, Angelin B, Rudling M. Of mice and men: Murine bile acids explain species differences in the regulation of bile acid and cholesterol metabolism. J Lipid Res. 2020;61:480–91.
129. Schubert K, Olde Damink SWM, von Bergen M, Schaap FG. Interactions between bile salts, gut microbiota, and hepatic innate immunity. Immunol Rev. 2017;279:23–35.
130. Jansen PLM, Strautnieks SS, Jacquemin E, Hadchouel M, Sokal EM, Hooiveld GJEJ, et al. Hepatocanalicular bile salt export pump deficiency in patients with progressive familial intrahepatic cholestasis. Gastroenterology. 1999;117:1370–9.
131. Dilger K, Hohenester S, Winkler-Budenhofer U, Bastiaansen BAJ, Schaap FG, Rust C, et al. Effect of ursodeoxycholic acid on bile acid profiles and intestinal detoxification machinery in primary biliary cirrhosis and health. J Hepatol. 2012;57:133–40.
132. Zou M, Wang A, Wei J, Cai H, Yu Z, Zhang L, et al. An insight into the mechanism and molecular basis of dysfunctional immune response involved in cholestasis. Int Immunopharmacol. 2021;92:107328.
133. Chen Y, Wang S, He M, Wang Y, Zhao H, Zhu H, et al. Prevalence of heterotypic tumor/immune cell-in-cell structure in vitro and in vivo leading to formation of aneuploidy. PLoS One. 2013;8:e59418.
134. Allen K, Jaeschke H, Copple BL. Bile acids induce inflammatory genes in hepatocytes: A novel mechanism of inflammation during obstructive cholestasis. Am J Pathol. 2011;178:175–86.
135. Gujral JS, Liu J, Farhood A, Jaeschke H. Reduced oncotic necrosis in Fas receptor-deficient C57BL/6J-lpr mice after bile duct ligation. Hepatology. 2004;40:998–1007.
136. Polzien F, Ramadori G. Increased intercellular adhesion molecule-1 serum concentration in cholestasis. J Hepatol. 1996;25:877–86.
137. Calmus Y, Arvieux C, Gane P, Boucher E, Nordlinger B, Rouger P, et al. Cholestasis induces major histocompatibility complex class I expression in hepatocytes. Gastroenterology. 1992;102:1371–7.
138. Hang S, Paik D, Yao L, Kim E, Trinath J, Lu J, et al. Bile acid metabolites control T(H)17 and T(reg) cell differentiation. Nature. 2019;576:143–8.
139. Kuipers F, de Boer JF, Staels B. Microbiome modulation of the host adaptive immunity through bile acid modification. Cell Metab. 2020;31:445–7.
140. Song X, Sun X, Oh SF, Wu M, Zhang Y, Zheng W, et al. Microbial bile acid metabolites modulate gut RORgamma(+) regulatory T cell homeostasis. Nature. 2020;577:410–5.

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141. Campbell C, McKenney PT, Konstantinovsky D, Isaeva OI, Schizas M, Verter J, et al. Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells. Nature. 2020;581:475–9.
142. Chen ML, Huang X, Wang H, Hegner C, Liu Y, Shang J, et al. CAR directs T cell adaptation to bile acids in the small intestine. Nature. 2021;593:147–51.
143. Zimmermann HW, Seidler S, Gassler N, Nattermann J, Luedde T, Trautwein C, et al. Interleukin-8 is activated in patients with chronic liver diseases and associated with hepatic macrophage accumulation in human liver fibrosis. PloS One. 2011;6:e21381.
144. Zimmermann HW, Seidler S, Nattermann J, Gassler N, Hellerbrand C, Zernecke A, et al. Functional contribution of elevated circulating and hepatic non-classical CD14CD16 monocytes to inflammation and human liver fibrosis. PLoS One. 2010;5:e11049.
145. Liang Y, Yang Z, Li C, Zhu Y, Zhang L, Zhong R. Characterisation of TNF-related apoptosis-inducing ligand in peripheral blood in patients with primary biliary cirrhosis. Clin Exp Med. 2008;8:1–7.
146. Kahraman A, Barreyro FJ, Bronk SF, Werneburg NW, Mott JL, Akazawa Y, et al. TRAIL mediates liver injury by the innate immune system in the bile duct-ligated mouse. Hepatology (Baltimore, Md). 2008;47:1317–30.
147. Sun JC, Lopez-Verges S, Kim CC, DeRisi JL, Lanier LL. NK cells and immune "memory". Journal of immunology (Baltimore, Md: 1950). 2011;186:1891–7. https://doi.org:10.4049/jimmunol.1003035
148. Diaz-Salazar C, Bou-Puerto R, Mujal AM, Lau CM, von Hoesslin M, Zehn D, et al. Cell-intrinsic adrenergic signaling controls the adaptive NK cell response to viral infection. J Exp Med. 2020;217:e20190549.
149. Sheppard S, Sun JC. Virus-specific NK cell memory. J Exp Med. 2021;218:e20201731.
150. Hydes TJ, Blunt MD, Naftel J, Vallejo AF, Seumois G, Wang A, et al. Constitutive activation of natural killer cells in primary biliary cholangitis. Front Immunol. 2019;10:2633.
151. Shimoda S, Hisamoto S, Harada K, Iwasaka S, Chong Y, Nakamura M, et al. Natural killer cells regulate T cell immune responses in primary biliary cirrhosis. Hepatology (Baltimore, Md). 2015;62:1817–27.
152. Böttcher K, Rombouts K, Saffioti F, Roccarina D, Rosselli M, Hall A, et al. MAIT cells are chronically activated in patients with autoimmune liver disease and promote profibrogenic hepatic stellate cell activation. Hepatology. 2018;68:172–86.
153. Jiang X, Lian M, Li Y, Zhang W, Wang Q, Wei Y, et al. The immunobiology of mucosal-associated invariant T cell (MAIT) function in primary biliary cholangitis: Regulation by cholic acid-induced Interleukin-7. J Autoimmun. 2018;90:64–75.
154. Kita H, Naidenko OV, Kronenberg M, Ansari AA, Rogers P, He XS, et al. Quantitation and phenotypic analysis of natural killer T cells in primary biliary cirrhosis using a human CD1d tetramer. Gastroenterology. 2002;123:1031–43.
155. Tse SW, Radtke AJ, Espinosa DA, Cockburn IA, Zavala F. The chemokine receptor CXCR6 is required for the maintenance of liver memory CD8(+) T cells specific for infectious pathogens. J Infect Dis. 2014;210:1508–16.
156. Heydtmann M, Lalor PF, Eksteen JA, Hübscher SG, Briskin M, Adams DH. CXC chemokine ligand 16 promotes integrin-mediated adhesion of liver-infiltrating lymphocytes to cholangiocytes and hepatocytes within the inflamed human liver. J Immunol. 2005;174:1055–62.
157. Lleo A, Gershwin ME, Mantovani A, Invernizzi P. Towards common denominators in primary biliary cirrhosis: The role of IL-12. J Hepatol. 2012;56:731–3.
158. Bae HR, Leung PSC, Hodge DL, Fenimore JM, Jeon SM, Thovarai V, et al. Multi-omics: Differential expression of IFN-gamma results in distinctive mechanistic features linking chronic inflammation, gut dysbiosis, and autoimmune diseases. J Autoimmun. 2020;111:102436.
159. Hodge DL, Berthet C, Coppola V, Kastenmüller W, Buschman MD, Schaughency PM, et al. IFN-gamma AU-rich element removal promotes chronic IFN-gamma expression and autoimmunity in mice. J Autoimmun. 2014;53:33–45.
160. Harada K, Shimoda S, Sato Y, Isse K, Ikeda H, Nakanuma Y. Periductal interleukin-17 production in association with biliary innate immunity contributes to the pathogenesis of cholangiopathy in primary biliary cirrhosis. Clin Exp Immunol. 2009;157:261–70.
161. Lan RYZ, Salunga TL, Tsuneyama K, Lian ZX, Yang GX, Hsu W, et al. Hepatic IL-17 responses in human and murine primary biliary cirrhosis. J Autoimmun. 2009;32:43–51.
162. Rong G, Zhou Y, Xiong Y, Zhou L, Geng H, Jiang T, et al. Imbalance between T helper type 17 and T regulatory cells in patients with primary biliary cirrhosis: The serum cytokine profile and peripheral cell population. Clin Exp Immunol. 2009;156:217–25.
163. Kawata K, Tsuda M, Yang GX, Zhang W, Tanaka H, Tsuneyama K, et al. Identification of potential cytokine pathways for therapeutic intervention in murine primary biliary cirrhosis. PLoS One. 2013;8:e74225.
164. Yang W, Yao Y, Yang YQ, Lu FT, Li L, Wang YH, et al. Differential modulation by IL-17A of cholangitis versus colitis in IL-2Ralpha deleted mice. PLoS One. 2014;9:e105351.
165. Chan CW, Chen HW, Wang YW, Lin CI, Chuang YH. IL-21, not IL-17A, exacerbates murine primary biliary cholangitis. Clin Exp Immunol. 2024;215:137–47.
166. Yang GX, Lian ZX, Chuang YH, Moritoki Y, Lan RY, Wakabayashi K, et al. Adoptive transfer of CD8(+) T cells from transforming growth factor beta receptor type II (dominant negative form) induces autoimmune cholangitis in mice. Hepatology. 2008;47:1974–82.
167. Yang GX, Wu Y, Tsukamoto H, Leung PS, Lian ZX, Rainbow DB, et al. CD8 T cells mediate direct biliary ductule damage in nonobese diabetic autoimmune biliary disease. J Immunol. 2011;186:1259–67.
168. Li Y, Li B, You Z, Zhang J, Wei Y, Li Y, et al. Cytotoxic KLRG1 expressing lymphocytes invade portal tracts in primary biliary cholangitis. J Autoimmun. 2019;103:102293.
169. Tsuda M, Ambrosini YM, Zhang W, Yang GX, Ando Y, Rong G, et al. Fine phenotypic and functional characterization of effector cluster of differentiation 8 positive T cells in human patients with primary biliary cirrhosis. Hepatology. 2011;54:1293–302.
170. Tsuda M, Ambrosini Y, Moritoki Y, Yoshida K, Zhang W, Yang GX, et al. CD45ROhighCD57+CD8high T cells in primary biliary cirrhosis (101.4). J Immunol. 2011;186:101.104–.
171. Huang B, Lyu Z, Qian Q, Chen Y, Zhang J, Li B, et al. NUDT1 promotes the accumulation and longevity of CD103. J Hepatol. 2022;77:1311–24.
172. Zhu HX, Yang SH, Gao CY, Bian ZH, Chen XM, Huang RR, et al. Targeting pathogenic CD8(+) tissue-resident T cells with chimeric antigen receptor therapy in murine autoimmune cholangitis. Nat Commun. 2024;15:2936.
173. Mitchison HC, Bassendine MF, Malcolm AJ, Watson AJ, Record CO, James OFW. A pilot, double-blind, controlled 1-year trial of prednisolone treatment in primary biliary cirrhosis: Hepatic improvement but greater bone loss. Hepatology (Baltimore, Md). 1989;10:420–9.
174. Leuschner M, Güldütuna S, You T, Hübner K, Bhatti S, Leuschner U. Ursodeoxycholic acid and prednisolone versus ursodeoxycholic acid and placebo in the treatment of early stages of primary biliary cirrhosis. J Hepatol. 1996;25:49–57.
175. Epstein O, Lee R, Boss AM, Jain S, Cook D, Scheuer P, et al. D-penicillamine treatment improves survival in primary biliary cirrhosis. Lancet (London, England). 1981;317:1275–7.

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176. Kaplan MM, Alling DW, Zimmerman HJ, Wolfe HJ, Sepersky RA, Hirsch GS, et al. A prospective trial of colchicine for primary biliary cirrhosis. N Engl J Med. 1986;315:1448–54.
177. Mason AL, Lindor KD, Bacon BR, Vincent C, Neuberger JM, Wasilenko ST. Clinical trial: Randomized controlled study of zidovudine and lamivudine for patients with primary biliary cirrhosis stabilized on ursodiol. Aliment Pharmacol Ther. 2008; 28:886–94.
178. Kaplan MM, Bonder A, Ruthazer R, Bonis PA. Methotrexate in patients with primary biliary cirrhosis who respond incompletely to treatment with ursodeoxycholic acid. Dig Dis Sci. 2010;55: 3207–17.
179. Christensen E, Neuberger J, Crowe J, Altman DG, Popper H, Portmann B, et al. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis. Final results of an international trial. Gastroenterology. 1985;89: 1084–91.
180. Tsuda M, Moritoki Y, Lian ZX, Zhang W, Yoshida K, Wakabayashi K, et al. Biochemical and immunologic effects of rituximab in patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. Hepatology (Baltimore, Md). 2012;55:512–21.
181. Hirschfield GM, Gershwin ME, Strauss R, Mayo MJ, Levy C, Zou B, et al. Ustekinumab for patients with primary biliary cholangitis who have an inadequate response to ursodeoxycholic acid: A proof-of-concept study. Hepatology (Baltimore, Md). 2016;64:189–99.
182. Hirschfield GM, Gershwin ME, Strauss R, Mayo MJ, Levy C, Zou B, et al. P367 phase 2 study evaluating the efficacy and safety of ustekinumab in patients with primary biliary cirrhosis who had an inadequate response to ursodeoxycholic acid. J Hepatol. 2014;60:S189–90.
183. Montano-Loza AJ, Hansen BE, Corpechot C, Roccarina D, Thorburn D, Trivedi P, et al. Factors associated with recurrence of primary biliary cholangitis after liver transplantation and effects on graft and patient survival. Gastroenterology. 2019; 156:96–107 e101.
184. Terasaki S, Nakanuma Y, Ogino H, Unoura M, Kobayashi K. Hepatocellular and biliary expression of HLA antigens in primary biliary cirrhosis before and after ursodeoxycholic acid therapy. Am J Gastroenterol. 1991;86: 1194–9.
185. Poupon R. Ursodeoxycholic acid and bile-acid mimetics as therapeutic agents for cholestatic liver diseases: An overview of their mechanisms of action. Clin Res Hepatol Gastroenterol. 2012;36(suppl 1):S3–12.
186. Nishigaki Y, Ohnishi H, Moriwaki H, Muto Y. Ursodeoxycholic acid corrects defective natural killer activity by inhibiting prostaglandin E2 production in primary biliary cirrhosis. Dig Dis Sci. 1996;41:1487–93.
187. McMahan RH, Wang XX, Cheng LL, Krisko T, Smith M, El Kasmi K, et al. Bile acid receptor activation modulates hepatic monocyte activity and improves nonalcoholic fatty liver disease. J Biol Chem. 2013;288:11761–70.
188. Verbeke L, Farre R, Verbinnen B, Covens K, Vanuytsel T, Verhaegen J, et al. The FXR agonist obeticholic acid prevents gut barrier dysfunction and bacterial translocation in cholestatic rats. Am J Pathol. 2015;185:409–19.
189. Christofides A, Konstantinidou E, Jani C, Boussiotis VA. The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. Metabolism. 2021;114:154338.
190. Colapietro F, Gershwin ME, Lleo A. PPAR agonists for the treatment of primary biliary cholangitis: Old and new tales. J Transl Autoimmun. 2023;6:100188.
191. Merkt W, Lorenz HM, Schmitt M. CAR T-cell therapy in autoimmune disease. N Engl J Med. 2024;390:1628–9.
192. Dong S, Hiam-Galvez KJ, Mowery CT, Herold KC, Gitelman SE, Esensten JH, et al. The effect of low-dose IL-2 and Treg adoptive cell therapy in patients with type 1 diabetes. JCI Insight. 2021;6:e147474.
193. McGovern JL, Wright GP, Stauss HJ. Engineering specificity and function of therapeutic regulatory T cells. Front Immunol. 2017;8:1517.
194. Akamatsu M, Mikami N, Ohkura N, Kawakami R, Kitagawa Y, Sugimoto A, et al. Conversion of antigen-specific effector/ memory T cells into Foxp3-expressing T(reg) cells by inhibition of CDK8/19. Sci Immunol. 2019;4:eaaw2707.

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