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Review Article

Targeting Gut Microbiota for the Treatment of Primary Biliary Cholangitis: From Bench to Bedside

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Abstract

Primary biliary cholangitis (PBC) is a complex cholestatic liver disease with an unresolved etiology. The gut microbiota is composed of a dynamic community of bacteria, archaea, fungi, and viruses that have a key role in physiological processes related to nutrition, immunity, and host defense responses. A number of recent studies found that the composition of the gut microbiota of PBC patients was significantly altered, and reported that gut dysbiosis might arise during PBC development because of the close interactions of the liver and the gut. In light of the growing interest in this topic, the focus of this review is to characterize PBC gut microbiota alterations, the correlation between PBC pathology and the gut microbiota, and prospective therapies that target the altered gut microbiota, such as probiotics and fecal microbiota transplantation.

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Introduction

Primary biliary cholangitis (PBC) is a cholestatic liver disease characterized by chronic nonsuppurative destructive lymphocytic cholangitis, specific antimitochondrial antibodies (AMAs), and a female predominance.[1] It is found in most regions of the world, and both its incidence and prevalence are rising globally.[2] Even though the PBC condition usually progresses slowly, it adversely impacts patient overall well being and gives rise to liver fibrosis and eventually cirrhosis.[3] To date, the pathophysiology of PBC is still poorly understood. Genetic predisposition, immune dysregulation, and environmental risk factors are thought to act together in PBC development.[4] Numerous studies[5–13] focusing on the gut-liver axis have reported that gut microbiota dysbiosis was linked to the pathophysiology of PBC.

The gut, which accounts for the majority of the human microbiome, is the least understood of the four host tissues, the gut, oral cavity, vagina, and skin.[14] The gut microbiota consists of a dynamic collection of bacteria, archaea, fungi, and viruses that are active in numerous host physiological functions, such as digestion, metabolism, resistance to pathogenic infections, and the maturation of immunity.[15] Hence, even slight alterations in the gut microbiota might negatively impact organismal health at different levels. Not surprisingly, gut dysbiosis has been cited as a major contributor to the pathological process of autoimmune liver diseases, such as primary sclerosing cholangitis (PSC) and PBC.[16]

Currently, the first-line medication for PBC treatment is ursodeoxycholic acid (UDCA). However, approximately 40% of the patients respond poorly.[1] An increasing number of studies[5–13,16] have established that the pathogenesis of PBC depends heavily on the gut microbiota, making the gut microbiota a promising novel PBC diagnostic and therapeutic target. Therefore, more emphasis should be placed on further exploring the specific influence of gut microbiota on PBC, as well as its relevant pathogenetic mechanisms and potential therapies. We searched the MEDLINE literature database through PubMed for the purpose of review by entering keywords, including "gut microbiota," "microbiota," "gut," "PBC," "primary biliary cholangitis," and "cholestatic liver disease".

Gut-liver axis

The gut-liver axis was initially characterized in 1987[17] and was first reported to be implicated in liver pathogenesis in 1998.[18] The portal vein and the bile acid enterohepatic circulation establish bidirectional communication of the gut-liver axis, in which the liver directly receives gut-derived products.[14,19] In healthy conditions, the liver's innate immune system is robust, allowing it to maintain immune tolerance against gut-derived antigens.[20] However, in the context of gut dysbiosis or gut leakiness, pathogenic bacteria or me-

Keywords: Primary biliary cholangitis; Gut microbiota; Lipopolysaccharides; Bile acids; Probiotics; Fecal microbiota transplantation.

Abbreviations: AMA, anti-mitochondrial antibody; ASBT, apical sodium-dependent bile acid transporter; BEC, bile duct epithelial cell; BSH, bile salt hydrolase; CYP7A1, cholesterol 7-alpha-hydroxylase; FXR, farnesoid X receptor; FGF, fibroblast growth factor; FMT, fecal microbiota transplantation; GF, germ-free; IL, interleukin; IgA, immunoglobulin A; IBD, inflammatory bowel disease; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa-B; NAFLD, nonalcoholic fatty liver disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PBMC, peripheral blood mononuclear cell; PPAR, peroxisome proliferator-activated receptor; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; TβMCA, taurine-conjugated β-muricholic acid; Th, T helper; UDCA, ursodeoxycholic acid; UTI, urinary tract infection.

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tabolites that translocate to the liver induce corresponding immune responses that subsequently lead to liver damage.[21] As the gut-liver axis has come to light as a major contributor to the occurrence and development of hepatobiliary disorders,[22] a better understanding of it will help shed light on the relevant processes by which gut dysbiosis impacts PBC.

Association between gut microbiota and PBC

PBC has a significant association with the gut microbiota, as patients with recurrent urinary tract infections (UTIs) are more likely to develop PBC.[23,24] Animal models of chronic bacterial exposure were shown to induce autoantibody production and PBC-like histological features.[25] In addition, female dnTGF*β*RII mice, a transgenic murine model of PBC, had more severe phenotypes than male mice, and they could be reversed by oral antibiotic therapy.[26] The aforementioned data suggest a strong link between the etiology of PBC and gut microbiota.

Furthermore, several studies[5–13] have demonstrated that, compared with healthy controls, bacterial diversity declined and the overall gut microbiota composition was significantly changed in PBC patients and animal models (Table 1).[5,7-13] Overall, the abundance of beneficial bacteria was decreased in PBC, while the abundance of opportunistic pathogens increased. At the phylum level, Firmicutes and Proteobacteria were over-represented in PBC, whereas Bacteroidetes were significantly decreased.[5,11,13] At the genus level, compared with healthy controls, patients with PBC had an increased abundance of *Sphingomonas*, *Haemophilus*, *Veillonella*, *Clostridium*, *Lactobacillus*, *Streptococcus*, *Bifidobacterium*, *Pseudomonas*, *Curvibacter*, *Klebsiella*, *Enterobacteriaceae,g*, *Carnobacterium*, *Megasphaera micronuciformis*, *Anaeroglobus geminatus*, *γ-Proteobacteria*, *Spirochaetaceae*, *Actinobacillus pleuropneumoniae*, *Paraprevotella clara*, *Methylobacterium*, *Acinetobacter*, and *Clostridiaceae* and a decreased abundance of *Leptotrichia*, *Bacteroides*, *Atopobium*, *Sutterella*, *Bulleidia*, *Oscillospira*, *Faecalibacterium*, *Acidobacteria*, *Lachnobacterium*, *Bacteroides eggerthii*, *Ruminococcus bromii*, *Morganella*, *Lautropia*, *Mogibacterium*, *Eikenella*, *Paludibacter*, and *F16,g*.[7–9,11–13] Remarkably, PBC patients who were stratified by their total bilirubin and albumin levels in the serum showed no meaningful difference in bacterial diversity and the relative abundance of the associated PBC taxa.[11] Yet, the taxonomic analysis of fecal microbes from PBC patients with or without advanced fibrosis revealed a reduced alpha diversity, an increase in *Weissella*, and a unique microbiota composition in PBC patients with advanced fibrosis compared with patients without advanced fibrosis.[10] In addition to the taxonomic analysis of fecal and mucosal samples from PBC patients, it is important to note that patients with a history of recurrent UTIs are more likely to develop PBC.[23] Further, *Escherichia coli* was the most common pathogen isolated from patients with UTIs.[24] It was also a key factor resulting from the production of AMAs,[27] highlighting its role in the pathogenesis of PBC.

Some specific microbiota were reported as probably associated with PBC. For example, increased bacterial invasion of epithelial was ascribed to the elevated abundance of two genera, *Enterobacter* and *Klebsiella* in family *Enterobacteriaceae*.[11] Chronic nonsuppurative destructive cholangitis was linked to *Sphingomonadaceae* abundance in PBC.[9] Furthermore, some altered microbiota were positively linked to liver function and serum cytokines in PBC patients,[11,13] such as *Veillonella* with interleukin (IL)-18 and IL16, *Megasphaera micronuciformis* and *Enterobacter asburiae* with IL18, *Klebsiella* with IL2A and total bilirubin, and *Eggerthella* sp. with direct bilirubin. Such correlations indicate that the microbes may be associated with disease states. In addition, some microbiota may act indirectly in PBC patients by modulating metabolites, such as indoleacrylate, which is produced by gut bacteria through tryptophan degradation and can trigger endothelial dysfunction and leukocyte activation.[13] Indoleacrylate, enriched in the urine and feces of PBC patients, has been found to be positively correlated with enrichment of the genera *Neisseriaceae* and *Klebsiella* in PBC,[13] suggesting that the two genera may be related to indoleacrylate-related signaling pathways and act together on the development of PBC. However, it still needs to be explicitly proven in future studies using the correct methods.

In summary, patients with PBC have decreased bacterial diversity and significantly different gut microbiota composition. Of note, some specific alterations of gut microbiota have a close association with the emergence of PBC.

Potential mechanisms that affect the gut microbiota in PBC

Production of metabolites

The gut microbiota, also known as "the new vital metabolic organ", is essential for human well-being.[28] Therefore it is unavoidable that any perturbation of the gut microbiota may adversely affect the body. For instance, accumulation of microbial products in the liver, such as lipopolysaccharide (LPS), leads to tissue damage by triggering inappropriate inflammatory immune responses, and impaired microbial bile-acid metabolism can result in cholestasis and liver disorder. The potential role of these two metabolites, LPS and bile acids, in the pathogenesis of PBC is summarized below.

LPS

LPS, the primary element of the Gram-negative bacterial outer membrane, consists of lipid A, core polysaccharide, and O-antigen, wherein lipid A is linked to the virulence of Gram-negative bacterial infections.[29] LPS affects the immune system by activating Toll-like receptor 4 (TLR4),[30] a pattern recognition receptor that confers resistance against pathogens infections and bridges innate and adaptive immunity.[31,32] Low doses of LPS build a nonspecific antibacterial and antiviral defense, whereas high doses can induce inappropriate or excessive immune activation that leads to cellular injury and multiple organ damage.[29] The liver is able to directly receive gut-derived products, such as pathogens, LPS, and nutrients, via the portal vein because to its anatomical location. Under healthy conditions, the liver exhibits no indication of immune response because of low hepatic TLR4 expression and negative TLR4 signaling regulation.[33] Increasing evidence indicates that the LPS-TLR4 pathway is implicated in several diseases, including PBC, by activating inappropriate immune responses (Fig. 1).[34–36]

Compared with healthy controls, serum LPS levels were shown to be elevated in PBC patients, and were positively linked to serum alkaline phosphatase, total bilirubin, and γ-glutamyltransferase levels.[36] Increased LPS and TLR4 have also been reported in injured biliary epithelial cells (BECs), hepatocytes, and infiltrating inflammatory cells of patients with PBC.[34,36,37] Increased levels of LPS activated TLR4, contributing to liver injury by promoting the recruitment of myeloid differentiation factor 88 (MyD88), the activation of the pro-inflammatory nuclear factor kappa-B (NF- κB) pathway, and the release of pro-inflammatory factors IL1β, IL6, and tumor necrosis factor-alpha (TNF-α), which facilitate recruitment of effector lymphocytes CD4+T and CD8+T into the

Table 1. Change in gut microbiota associated with PBC

Participants	Sample origin	Comparison	Change of gut microbiota		Method	Ref
			Increased	Decreased		
dnTGFβRII mice; WT mice	Feces	PBC vs. Healthy	Firmicutes; Lachnospiraceae; Bacteroidaceae	Bacteroidetes; S24-7; Ruminococcaceae; Rikenellaceae; Porphyromonadaceae	16SrRNA; 454 Genome Sequencer FLX Titanium platform	Ma *et al*.[5]
PBC patients (n=42); Healthy controls (n=30)	Feces	PBC vs. Healthy	γ-Proteobacteria; *Spirochaetaceae*; *Enterobacteriaceae*; *Veillonella*; *Neisseriaceae*; *Enterobacter asburiae*; *Streptococcus*; Enterobacterasburiae; *Actinobacillus pleuropneumoniae*; *Anaeroglobus geminatus*; *Haemophilus parainfluenzae*; *Megasphaera micronuciformis*; *Paraprevotella Clara*; *Klebsiella*;	Acidobacteria; *Lachnobacterium sp.*; *Bacteroides eggerthii*; *Ruminococcus bromii*	16SrRNA; Illumina MiSeq	Lv *et al*.[13]
PBC patients (n=79); Healthy controls (n=114)	Feces	PBC vs. Healthy	*f-Enterobacteriaceae*; *Prevotella*; *Sneathia*; *Veillonella*; *Fusobacterium*; *Haemophilus*; *Streptococcus*; *Pseudomonas*; *f-Clostridiaceae*; *Citrobacter*; *Lactobacillus*; *Salmonella*; *Clostridium*; *Klebsiella*;	*Bacteroides*; *f-Mogibacteriaceae*; *Blautia*; *f-Christensenellaceae*; *Butyricimonas*; *Akkermansia*; *Odoribacter*; *Dialister*; *f-S24-7*; *f-Rikenellaceae*; *Oscillospira*; *Faecalibacterium*; *Sutterella*	16SrRNA; Illumina MiSeq	Chen *et al*.[12]
PBC patients (n=60); Healthy controls (n=80)	Feces	PBC vs. Healthy	Fusobacteria; Proteobacteria spp; *Haemophilus*; *Veillonella*; *Klebsiella*; *Clostridium*; *Lactobacillus*; *Streptococcus*; *Pseudomonas*; *Enterobacteriaceae,g*;	Bacteroidetes spp; *Sutterella*; *Oscillospira*; *Faecalibacterium*	16SrRNA; Illumina MiSeq	Tang *et al*.[11]
PBC patients (n=23)	Feces	PBC patients with advanced fibrosis (15) vs. with non-advanced fibrosis (8)	*Weissella*		16SrRNA; Illumina MiSeq	Lammert *et al*.[10]
PBC patients(n=34); Healthy controls (n=21)	Ileal mucosa	PBC vs. Healthy	*Sphingomonas*; *Pseudomonas*; *Methylobacterium*; *Carnobacterium*; *Acinetobacter*; *Curvibacter*; *Clostridiaceae*;	*Leptotrichia*; *Morganella*; *Eikenella*; *Lautropia*; *Bulleidia*; *Atopobium*; *Paludibacter*; *Mogibacterium*; an unknown genus belonging to the class *TM7_3*; *F16,g* (an unknown genus of the family *F16*)	16SrRNA; Illumina MiSeq	Kitahata *et al*.[9]
PBC patients (n=76); Healthy controls (n=23)	Feces	PBC vs. Healthy	*Streptococcus*; *Lactobacillus*; *Bifidobacterium*; *Enterococcus*;	*Lachnospiraceae*; *Ruminococcaceae*	16SrRNA; Illumina MiSeq	Furukawa *et al*.[8]
PBC patients (n=39); Healthy controls (n=15)	Feces; Saliva	PBC vs. Healthy	*Lactobacillales* in feces; *Eubacterium* and *Veillonella* in saliva;	*Clostridium subcluster XIVa* in feces; *Fusobacterium* in saliva;	16SrRNA; Terminal restriction fragment length polymorphism	Abe *et al*.[7]

Comparison of condition A vs. condition B: ↑signifies an increase in condition A relative to condition B; ↓signifies a decrease in condition A relative to condition B. PBC, primary biliary cholangitis; WT, wild type.

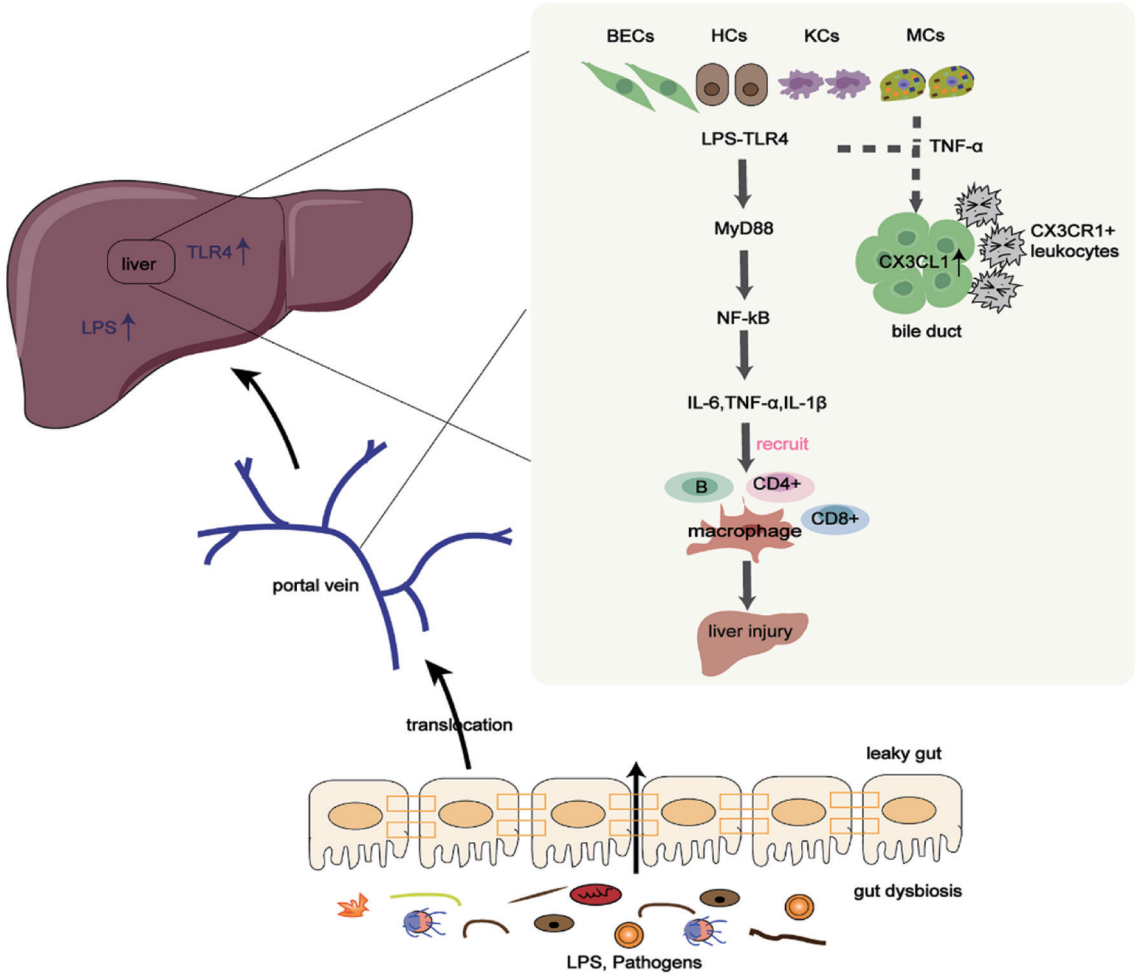

Fig. 1. Gut microbiota contributes to the pathogenesis of PBC through the LPS/TLR4 signaling pathway. Gut dysbiosis and increased gut permeability promote pathogens and metabolite translocation to the liver, contributing to liver injury through the LPS/TLR4 signaling pathway. In addition, sensitized monocytes and TNF-α stimulate BECs to upregulate CX3CL1, causing cholangitis by interacting with CX3CR1+ leukocytes. BECs, bile duct epithelial cells; HCs, hepatocytes; IL, interleukin; KCs, Kupffer cells; LPS, lipopolysaccharide; MCs, monocytes; MyD88, myeloid differentiation factor 88; NF- κB, nuclear factor kappa-B; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha.

portal tracts of PBC patients.[36,38–40] Beyond that, peripheral blood mononuclear cells (PBMCs) in PBC patients are also highly sensitive to LPS. Compared with healthy controls, PBMCs isolated from PBC patients produced higher levels of IL1β, IL6, IL8, and TNF-α after LPS stimulation.[36,41] Further, sensitized monocytes and TNF-α stimulated BECs to upregulate the chemokine-adhesion molecule CX_3CL1. Upregulation of CX_3CL1 in damaged bile ducts attracted CD4+T and CD8+T cells and interacted with CX_3CR1+ leukocytes to cause cholangitis.[42] In summary, the interaction between LPS and TLR4 and the upregulation of CX_3CL1 in the liver promote inflammatory immune responses, causing the breakdown of local immune tolerance and liver injury.

Bile acids

Bile acids, the primary functional elements of bile, are synthesized in the liver from cholesterol via classical and unconventional pathways.[43] After meals, bile acids are released into the small intestine to facilitate digestion and absorption of dietary lipids.[44] Approximately 95% of the bile acids are actively reabsorbed and delivered back to the liver by portal circulation.[45] The remaining 5% of bile acids are modified by various bacterial transformations, with a portion passively reabsorbed into the liver and the rest lost in the feces.[46] Some bile acids are harmful to the organism. For instance, hydrophobic bile acids are considered to be hepatotoxic, leading to irreversible hepatocyte death by inducing mitochondrial oxidative stress and ER stress, with increased mitochondrial permeability.[43,47] Conversely, bile acids have well-known antimicrobial properties and subsequently affect the gut microbial composition.[46,48] The loss of secondary bile acids is related to susceptibility to pathogens infections, which was reversed by restoring the secondary bile acid pool.[49] Taken together, the evidence of mutual regulation between bile acids and gut microbes is crucial for bile acid metabolism and microbiota composition, and perturbation may impact the pathophysiological processes of the host.

Evidence has shown that the serum and fecal bile acids profiles in PBC patients without UDCA treatment are significantly different from those of controls.[12] Particularly, PBC patients without UDCA treatment showed an increase in the ratio of conjugated/unconjugated bile acids and a decrease in the ratio of secondary/primary bile acids, indicating abnormal microbial bile-acid metabolism (Fig. 2). Importantly, variation

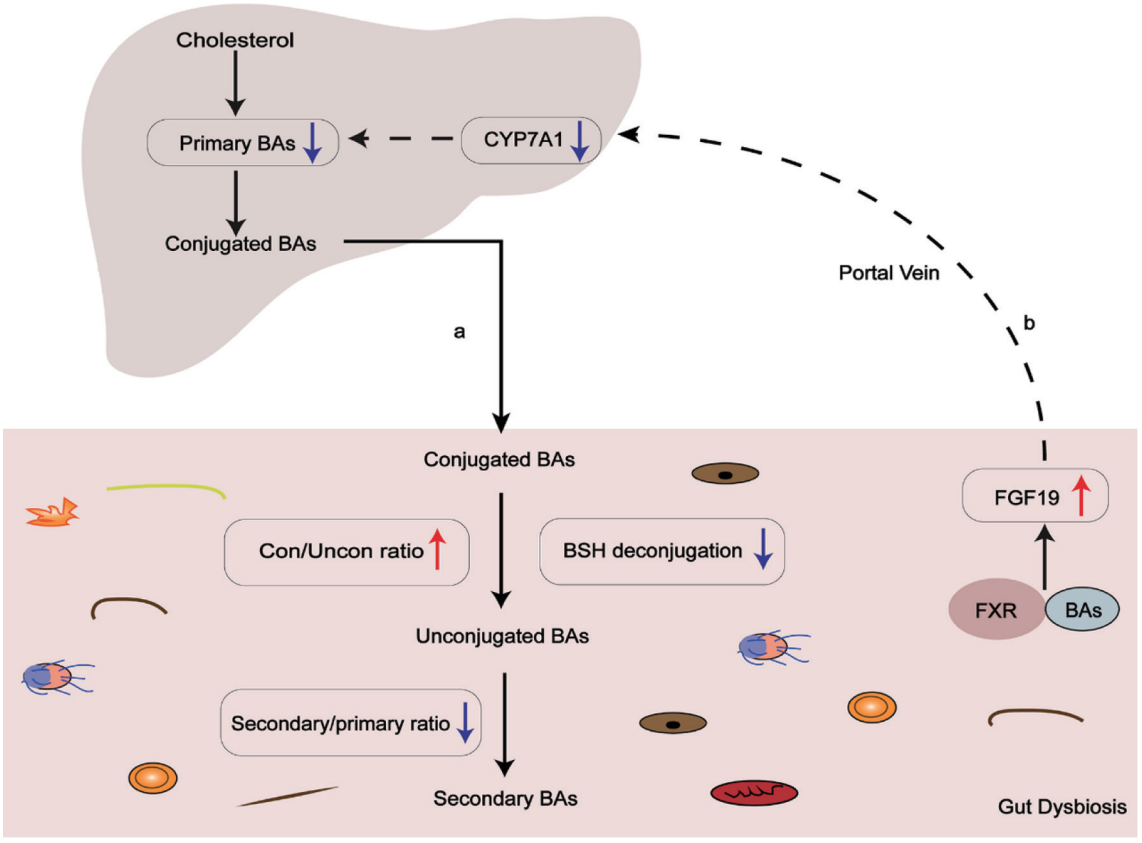

Fig. 2. Bile acid-microbiota interactions are impaired in PBC patients. (A) Gut dysbiosis and decreased BSH deconjugation result in impaired microbial bile acid metabolism, particularly an increase in the ratio of conjugated/unconjugated bile acids and a decrease in the ratio of secondary/primary bile acids. (B) Serum FGF19 is elevated in patients with PBC, further inhibiting CYP7A1 transcription and bile acid synthesis. BAs, bile acids; BSH, bile salt hydrolase; CYP7A1, cholesterol 7-alpha-hydroxylase; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor.

in bile acids pool of PBC patients was linked to gut dysbiosis. For instance, the level of secondary bile acids was negatively associated with genera that were enriched in PBC (*Veillonella*, *Klebsiella*), and positively associated with genera enriched in controls (*Bacillus* spp, *Oscillatory* spp).[12] It is widely accepted that conversion of bile acids remaining in the intestine is primarily dependent on the activity of microbial enzymes.[50,51] For example, bile salt hydrolases (BSHs), which are present in all major bacteria in the human intestine, including *Bacteroides*, *lactobacilli*, *bifidobacteria*, and *Clostridium*, deconjugate bile acids to unconjugated forms for further modification, which is the first step of bile acid metabolism in the intestine.[52] Therefore, alterations of bile acids are likely the result of changes in the gut microbiota composition in PBC and subsequently dysfunction of the responsible microbial enzymes leads to lack of bile acid conversion. Conversely, because of the antimicrobial properties of bile acids, it is plausible that alterations of bile acids in PBC may profoundly affect microbial composition. Indeed, cholestyramine treatment modulated endogenous bile acids in PBC patients and had benefits associated with changes in gut microbiota and their metabolites.[53]

In addition to the abnormal microbial bile acid metabolism described above, the gut microbiota also suppress bile acid synthesis by regulating the bile acid receptor farnesoid X receptor (FXR). FXR is a bile acid sensor that acts to regulate bile acid synthesis and homeostasis together with its downstream effector, fibroblast growth factor (FGF) 15/19.[54] A recent study showed that in conventionally raised mice, bile acid synthesis was inhibited because of the alleviation of ileum FXR inhibition.[55] Bile acid levels were dramatically lowered in the gallbladder compared with germ-free (GF) mice due to the presence of gut microbiota, especially the level of taurine-conjugated β-muricholic acid (TβMCA), which is an FXR antagonist. Decreased levels of TβMCA activated FXR and increased the downstream expression of FGF15, leading to the suppression of cholesterol 7-alpha-hydroxylase (CYP7A1)-mediated bile acid synthesis.[55] Another study reported that FXR antagonists cannot be metabolized without gut bacteria.[56] Along line, the gut microbiota might modulate bile acid biosynthesis by altering the bile acid composition and by regulating the FXR-FGF15/19 negative feedback system. Furthermore, patients with PBC had increased serum FGF19 levels, suggesting that the bile acid pool composition was changed, which was consistent with a microbial bile acid metabolism disorder in PBC.[12] In summary, the gut microbiota and bile acids modulate each other. Any perturbation of the gut microbiota and bile acids may profoundly impact the organismal pathophysiology process. Significant alterations in gut microbiota composition and impaired microbial bile acids metabolism in PBC patients may account for disease consequences, such as cholestasis.

Others mechanisms

Molecular mimicry

PBC is an autoimmune liver disease with highly specific AMAs

that primarily target the mitochondrial PDC-E2 complex, but what triggers this autoimmune mechanism is unclear.[57,58] The involvement of molecular mimicry in the pathogenesis of PBC has been proposed, in which host cells recognize exogenous bacterial or viral epitopes and subsequently trigger AMA production and effector T-cell responses against their own proteins.[59,60] Streptococcus intermedius or Novosphingobium aromaticivorans exposure led to specific antibody production and liver injury resembling PBC in mice.[25,61] Furthermore, AMAs in the serum of PBC patients also crossed-react to bacterial proteins of *Escherichia coli* and *Novosphingobium aromaticivorans*.[59,62,63] Both showed the close cross-reactivity between the microbes and antibodies in PBC. Accordingly, a PBC hypothesis is based on the "leaky gut concept", in which the gut microbiota induces anti-PDC-E2 responses and biliary damage through the translocation of bacterial molecules and byproducts from the gut. Details of the molecular mimicry of microorganisms in PBC, including *E. coli*, *mycoplasma*, *lactobacilli*, *H. pylori*, and *Novosphingobium aromaticivorans*, have been extensively reviewed elsewhere, and some plausible mechanisms have been proposed.[64–68]

Regulation of gut permeability

Studies have revealed that gut permeability was increased in PBC patients,[69,70] but the cause of this increase remains poorly understood. It is well established that the intestinal commensal bacteria act as an innate immune barrier to resist pathogen infections together with mucins, antimicrobial peptides, and immunoglobulins.[22,71] Intestinal commensal bacteria, such as *Ruminococcaceae* and *Eubacterium*, affect gut barrier function by producing butyrate that can stimulate tight junctions and mucus production.[72] Also, microbes themselves impact the intestinal barrier function by controlling the production of tight junction proteins.[73] In that way, dysbiosis of the gut microbiota may disrupt tight junction and thereby increase gut permeability. As described above, *Ruminococcaceae* abundance was reduced in PBC patients, which might account for the increased gut permeability.[8,13] Furthermore, secreted immunoglobulin A (IgA), which contributes to gut microbiome composition and is essential for maintaining intestinal homeostasis,[74] was abnormal in the intestinal epithelium of PBC patients.[75] In addition, the presence of gut microbes can enhance gut permeability during cholestasis.[76] With compromised gut barrier function, gut-derived antigens translocate from the gut to mesenteric lymph nodes, extraintestinal organs, and the systematic circulation.[34,36,77] As previously stated, translocated products may trigger inflammatory immune responses through the LPS/TLR4 pathway in the liver of PBC patients or induce autoantibodies production by molecular mimicry, thereby leading to exacerbating liver damage.

PBC and intestinal mucosal immune activation

Intestinal mucosal immunity is essential for resisting pathogen infections and maintaining intestinal homeostasis. Its dysregulation has been implicated in autoimmune diseases.[78–80] The gut microbiota is required for intestinal mucosal immunity maturation,[81] and lack of gut microbiota in GF mice leads to immune system deficiency.[82–84] It is thus no surprise that gut dysbiosis can influence the intestinal mucosal immune balance. For example, gut dysbiosis increases inflammatory bowel disease (IBD) inflammation by inducing abnormal immune responses that are improved by active bacterial products.[85–88] Prebiotic treatment decreased the levels of the proinflammatory factors in the mesenteric lymph nodes in a mice model.[89] In addition, IL17-producing T helper (Th17) cells are associated with inflammatory disorders and are enriched in the liver and the gut.[90] In the gut, Th17 cells are maintained by commensal bacteria that induce the secretion of a factor, serum amyloid A, needed for Th17-specific IL17A expression,[91] which promotes inflammation via leucocyte recruitment.[92] Indeed, Th17 cells have been linked to PBC.[93] Given the significance of gut microbiota in intestinal mucosal immunity, it seems plausible to hypothesize that gut dysbiosis and imbalanced mucosal immunity contribute to the progression of PBC, warranting the emergence of new evidence.

Therapy

Knowing the importance of gut microbiota dysbiosis in PBC progression, treatments aimed at restoring the gut microbiota, such as the administration of probiotics, fecal microbiota transplantation (FMT), and the intervention of mechanistic pathways might benefit PBC patients. In addition, existing PBC medications, such as UDCA, treat the disease by both regulating bile acid metabolism and adjusting gut microbiota composition.

Probiotics

Probiotics are live, beneficial microorganisms that can help with a variety of diseases by promoting the balance of gut microbiota, improving metabolic profiles, and repairing intestinal barrier dysfunction.[94–96] For example, the administration of the probiotic VSL#3 to mice, and BSH-active *Lactobacillus reuteri* NCIMB 30242 in humans, was shown to improve microbial bile-acid metabolism by promoting the enrichment of BSH-retaining species, mainly *Lactobacillus* and *Bifidobacteria*, in the intestinal microbiota.[97,98] Furthermore, daily consumption of probiotic rich foods, such as yogurt, had positive outcomes in patients with nonalcoholic fatty liver disease (NAFLD).[99] Along those lines, it is reasonable that probiotics treatment is beneficial for patients with PBC despite the lack of published evidence and warrants further study.

FMT

FMT is emerging as a way to restore healthy microbiota by transferring a fecal suspension from a healthy donor to the digestive system of a patient.[100] In addition to treating recurrent *Clostridium difficile* infections, FMT has been found to be beneficial for autoimmune diseases, such as PSC.[101–103] FMT restores gut microbiota diversity and improves biochemical indicators in patients with PSC, but needs to be validated in large study cohorts. Although FMT treatment has not been studied in PBC patients, it is intriguing to attempt that in future studies.

Intervention pathway in pathogenesis

As defective microbial bile acid metabolism and aberrant immune responses have been found in PBC, the focus is on reestablishing disrupted microbial bile acid metabolism, inhibiting abnormal immune responses, or preserving immune tolerance.[1] Drugs other than UDCA and obeticholic acid (OCA) for treating PBC are still in experimental or clinical stages. Currently, drugs targeting bile acids metabolism, including FXR agonists, apical sodium-dependent bile acid transporter (ASBT) inhibitors, and peroxisome proliferator-activated receptor (PPAR) agonists, delay disease progression by decreasing cytotoxicity and inflammation.[104] Furthermore, it is necessary to repair the damaged intestinal barrier to avoid inappropriate intestinal immune responses. Dietary therapies and anti-TNF-α drugs proposed for restoring gut permeability in IBD[105] might also be evaluated in

PBC in the future. Immunosuppressive therapy, long-term glucocorticoid treatment, and classical immunosuppressants have failed to provide significant benefits to PBC patients.[106] The development of B-cell, T-cell, and cytokine/chemokine-targeted treatments is accelerating. In addition, the use of nanomedicines to optimize treatment of autoimmune disease is under development, and has the potential to overcome many of the drawbacks of current immunosuppressive therapies.[107] The specific mechanisms of these drugs have been described in detail elsewhere.[104]

UDCA

The current first-line treatment for PBC patients is UDCA, which improves liver function and graft-free survival by several mechanisms, including enhancing the hydrophilicity of bile acid pools, immune modulation, anti-inflammatory properties, and antifibrotic properties.[108,109] Remarkably, UDCA might also adjust gut microbiota composition. Studies have shown that PBC patients treated with UDCA for 6 months had a partial restoration of gut dysbiosis, with a reduced abundance of *Haemophilus* spp, *Streptococcus* spp, and *Pseudomonas* spp that were enriched in PBC patients without UDCA treatment. UDCA also increased *Bacteroidetes* spp, *Oscillospira* spp and *Sutterella* spp, which were enriched in healthy controls.[11] In addition, bacteria *Bilophila* spp, which metabolizes taurine,[110] was elevated in patients after UDCA treatment, resulting in a reduction in taurine-conjugated bile acids and the conjugated/unconjugated ratio, which was associated with a decrease in liver enzyme levels.[11] Furthermore, UDCA increased the abundance of intestinal *Bacteroides* that express BSH, which is crucial for microbial bile acid metabolism, in pregnant intrahepatic cholestasis patients.[111] The evidence suggests UDCA treatment could potentially ameliorate PBC by modifying the gut microbiota composition, but, details of the mechanism of action of UDCA on the gut microbiota of the host are poorly understood and should be explored in future studies.

Conclusions

PBC is a cholestatic liver disease with an obscure etiology. Mounting evidence points to the significance of gut-liver crosstalk in PBC progression. Overall, there exist significant differences between PBC patients and healthy individuals in gut microbiota composition and microbial metabolite levels. Gut dysbiosis promotes hepatobiliary injury in PBC patients by several mechanisms, including influencing the intestinal mucosal immune balance, increasing gut permeability that in turn promotes bacterial translocation, inducing abnormal immune activation through the LPS/TLR4 signaling pathway and molecular mimicry mechanisms, and suppressing the microbial metabolism of bile acids. For patients who do not respond effectively to UDCA/OCA treatment, novel treatments such as probiotics, FMT, and some pharmacological agents targeting gut microbiota-associated pathways represent new avenues for improving PBC by restoring gut microbiota composition and modulating immune responses. Furthermore, it should be highlighted that numerous additional variables, such as nutrition, geographical location, and medications, affect the metataxonomic analysis of human gut microbes. Thus, we should also focus on inter-individual variation.

However, there are several limitations in existing microbiome research that should be addressed in the future. Firstly, the number of studies is too small to infer any meaningful association between microbiota composition and disease severity or to control for confounding factors, such as diet, drugs, and environment. Secondly, most feces samples do not completely reflect the profiles of mucosal communities. Finally, fungi and viruses should be considered even though they only make up a modest fraction of the gut microbiota. A better overall understanding of gut dysbiosis in PBC patients will help us have a better appreciation of the pathological mechanisms of PBC.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Collected the literature and drafted the manuscript (LZ), critically revised the manuscript (LY), and designed the concept and carried out the final revision of the manuscript (HC). All authors read and approved the final version of the manuscript.

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