Impact of Microbes on the Pathogenesis of Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC)

Jochen Mattner

Mikrobiologisches Institut—Klinische Mikrobiologie, Immunologie und Hygiene, Universitätsklinikum Erlangen and Friedrich-Alexander Universität (FAU) Erlangen-Nürnberg, Wasserturmstr. 3/5, D-91054 Erlangen, Germany; jochen.mattner@uk-erlangen.de; Tel.: +49-9131-85-23640; Fax: +49-9131-85-1001

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Abstract: Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent the major clinical entities of chronic cholestatic liver diseases. Both disorders are characterized by portal inflammation and slowly progress to obliterative fibrosis and eventually liver cirrhosis. Although immune-pathogenic mechanisms have been implicated in the pathogenesis of PBC and PSC, neither disorder is considered to be a classical autoimmune disease, as PSC and PBC patients do not respond to immune-suppressants. Furthermore, the decreased bile flow resulting from the immune-mediated tissue assault and the subsequent accumulation of toxic bile products in PBC and PSC not only perpetuates biliary epithelial damage, but also alters the composition of the intestinal and biliary microbiota and its mutual interactions with the host. Consistent with the close association of PSC and inflammatory bowel disease (IBD), the polyclonal hyper IgM response in PBC and (auto-)antibodies which cross-react to microbial antigens in both diseases, an expansion of individual microbes leads to shifts in the composition of the intestinal or biliary microbiota and a subsequent altered integrity of epithelial layers, promoting microbial translocation. These changes have been implicated in the pathogenesis of both devastating disorders. Thus, we will discuss here these recent findings in the context of novel and alternative therapeutic options.

Keywords: PSC; PBC; intestinal microbiota; bile acids

1. Introduction

The liver commands several central metabolic and synthetic pathways in the body. Among these is also the regulation of bile (acid) metabolism [1].

Bile is synthesized in the pericentral hepatocytes, drained through the bile ducts into the hepatic duct, and released into the duodenum by the sphincter of Oddi [2]. Bile acids—which constitute for half of the organic biliary compounds [2,3]—are conserved under physiologic conditions; about 95% of bile acids are reabsorbed by the intestinal epithelium and transported back through the portal vein system to the liver, where they are re-conjugated and re-secreted into the bile fluid (enterohepatic circulation) [4].

Bile acids themselves exhibit several fundamentally important functions [2,5]. These include the elimination of many waste products and catabolites such as cholesterol and bilirubin from the body via the feces, the adsorption and digestion of lipids and fat-soluble vitamins in the gut, and—together with immunoglobulin A (IgA) (which is secreted from the epithelium into the bile fluid)—potent anti-microbial properties that inhibit bacterial growth and adhesion, thus protecting against ascending infections within the biliary tract. However, as there exist multiple microbes which
are tolerant against bile [3], the anti-microbial effects of bile (acids) selectively restrain certain microbial species, and subsequently affect the composition of the complete intestinal or biliary microflora. Thus, an obstruction of the bile flow as it occurs in primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) alters the microbiota, the susceptibility to infection, and the integrity of the epithelial layers [6–8]. As the liver—due to its anatomic location within the blood circulation—is exposed to various nutritional and microbial compounds from the gastrointestinal tract, a metabolic and/or microbial distortion might promote inappropriate inflammatory immune reactions within hepatic tissues.

2. Mutual Interactions between the Bile and the Intestinal Microbiota

The diverse and complex microbial community within the gastrointestinal tract produces metabolites and extracts nutrients from a large range of molecules that enzymes of the host are unable to convert [9]. Many of these nutrients and metabolites derived from the commensal microbiota have been implicated in the development, homeostasis, and function of the immune system, suggesting that microbial commensals influence host immunity via nutrient- and metabolite-dependent mechanisms [10]. Novel findings suggested that—similar to the situation in the intestine—the gallbladder also harbors a complex microbiota, and that the biliary mucosa features a chemical, mechanical, and immunological barrier, ensuring immunological tolerance against microbial commensals [6].

The regulation of the bile acid pool is one example of the interference of the microbial metabolism with the host [11]. The microbiota can modify the remaining 5% of the total bile acid pool which are not absorbed by the epithelium in multiple ways [12]. The modifications of bile acids retained in the gut depend on the intestinal and biliary bile acid flow, the population of the respective mucosal tissues with bile-converting microbes, and the properties and activity of the responsible microbial enzymes [13]. The primary bile acids—cholic and chenodeoxycholic acid, for example—can be converted to more than 20 different secondary or tertiary bile acid metabolites by a particular subset of anaerobic bacteria in the gut [9,14]. For example, Ruminococcus can form ursodeoxycholic acid (UDCA) [15], a tertiary bile acid which is the only FDA-approved drug in the treatment of PBC. Furthermore, bacterial bile salt hydrolases (BSH), abundant enzymes found in all major bacterial phyla [16], deconjugate primary bile acids such as glycocholate or taurocholate to cholate, and profoundly alter both local, gastrointestinal, and systemic hepatic host functions; thus, gastrointestinal BSH expression results in local bile acid deconjugation with concomitant alterations in lipid and cholesterol metabolism, signaling functions, and weight gain [3,17–20]. On the other hand, the microbiota might metabolize the deliberated amino acids from deconjugation as an energy or metabolic source and/or increase their survival or tolerance to bile [3,21,22]. Both cholesterol and lipid metabolism are affected in PBC and PSC, resulting in vitamin deficiencies, distortions in bile acids, and perpetuation of biliary disease [23–27]. Probiotics have been suggested to increase bile acid synthesis and metabolism in humans and mice [28,29], and might therefore interfere with the described phenotypes, although further studies are required to delineate the distinct effects.

Conversely, bile acids control bacteria [30], exert anti-microbial properties [31], and thus modulate the microbiota both directly and indirectly through the activation of innate immune genes [32]. The loss of secondary bile acids, for example, has been associated with susceptibility to infection by pathogenic bacteria, and a restoration of the secondary bile acid pool promotes colonization resistance [33]. The decreased bile acid secretion in liver cirrhosis is associated with bacterial overgrowth in the gut [34,35]. Bile duct ligation also promotes bacterial proliferation and replication [36,37]. Along with the suppression of bacterial expansion in vivo, bile—predominantly the unconjugated bile acids therein—inhibit bacterial growth in vitro [3,38]. Long chain fatty acids (which are associated with bile acids in mixed micelles) likely contribute to the antimicrobial effects of bile fluid [39–41]. However, there exist several pathogenic microbial species which are tolerant against bile, such as Escherichia coli or Helicobacter spp. [42–46]. Furthermore, the composition of the bile fluid might be altered in PSC...
and PBC, allowing unusual bacteria to expand and/or even perpetuate ascending infections within the biliary tree. Thus, host metabolism can be affected through microbial modifications of bile acids, which lead to altered immune signaling via bile acid receptors, but also modified immune responses triggered by an altered microbiota composition. Further studies are needed to expand on these ideas.

3. Association of Distinct Bacteria with Primary Sclerosing Cholangitis (PSC) and Primary Biliary Cirrhosis (PBC)

There exist several indirect hints that microbes are involved in the pathogenesis of PBC and PSC: a polyclonal IgM response in PBC [47–49], which can be frequently observed during chronic infections; an increased risk of patients with recurrent urinary tract infections to develop PBC [50–55]; and the close association of PSC with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC) [56,57].

More direct hints include the linkage of different bacteria and viruses to the pathogenesis of PBC [58–63] and PSC [64,65]. Molecular mimicry has been proposed as one potential pathogenic mechanism underlying immune-mediated biliary damage. Thus, antibodies in the sera of PBC patients which bind to the mitochondrial E2 subunit of the pyruvate dehydrogenase complex (PDC-E2)—the signature antigen of PBC—also cross-react to conserved bacterial proteins [66–73]. These include the ATP (adenosine triphosphate)-dependent Clp protease of Escherichia coli, the β-galactosidase of Lactobacillus delbrueckii (a constituent of the vaginal flora), and two yet-undefined lipoylated proteins of Novosphingobium aromaticivorans, a ubiquitous α-proteobacterium also found at mucosal surfaces and in the feces of humans [66–71,74–76]. Furthermore, the infection of genetically susceptible mouse strains with Novosphingobium aromaticivorans induced anti-PDC E2 responses and liver lesions resembling PBC in humans [77–79]. Novosphingobium spp. can also metabolize xenobiotics [80–82], and thus interfere with enterohepatic bile acid cycling and hormone metabolism. All these characteristics and metabolic interactions might contribute to the break of self-tolerance within the unique immunological milieu of the liver [83]. As anti-PDC-E2 antibody responses precede the induction of liver pathology [84], the period between the detection of antibody responses and the onset of biliary pathology may mark a time frame in which an application of antibiotics may halt the development of full-blown PBC, assuming that the underlying pathogenic mechanisms are triggered by a bacterial infection. Furthermore, a microbial-mediated insult or a tissue-tropism of distinct microbes with homology to PDC-E2 might underlie the immune attack against biliary epithelial cells. Thus, immune responses against PDC-E2 might primarily target a microbe and not a mitochondrial enzyme. This would explain the tissue-specific pathology in PBC, although the hallmark antigen of PBC is ubiquitously expressed.

Bacteria have also been linked to the pathogenesis of PSC [64,65]. Given that the intestine is a key regulator of immunopathogenic T helper type 17 (Th17) cells [85], and that increased Th17 responses to pathogen stimulation in PSC patients have been reported [86], this may underpin a common disease mechanism of PSC and IBD, and open up novel treatment avenues based on rational targeting of immune pathways. Mucosal lymphocytes may also play a pivotal role in graft versus host disease affecting the liver, and there is increasing evidence to support dysregulated mucosal immunity as being responsible for the hepatic manifestations of gluten-sensitive enteropathy, graft versus host disease, as well as the pancreatobiliary manifestations of IgG4-related disease [85].

4. Changes in the Composition of the Microbiota in PBC and PSC Patients

Compared to the intestine, the microbiota of the biliary tract contains relatively lower levels of Bacteroidetes, but comparable amounts of Firmicutes. In contrast, the relative numbers of Proteobacteria, TM7, Tenericutes, Actinobacteria, and Cyanobacteria are increased [6,87]. However, as bile samples in these studies are frequently collected via endoscopic retrograde cholangio-pancreatography (ERCP), contaminations with the intestinal microbiota are likely.

Specific alterations of the biliary microbiota have been reported in PBC patients undergoing liver transplantation compared to patients undergoing cholecystectomy because of gastric cancer or
cholecystolithiasis, or an explanation for donor liver transplants [88]. The 16S-RNA-based analysis revealed an accumulation of Gram-positive cocci in the bile of PBC patients with end-stage disease, whereas Gram-negative bacteria were predominantly recovered from patients with cholecystolithiasis. In contrast, bacteria were detected just in 1 out of 12 patients who did not suffer from primary hepatobiliary disease. Thus, this study contrasts with an analysis of healthy pigs, in which a complex biliary microbiota was detected in all analyzed animals [89]. These discrepancies, as well as the question of whether changes in the biliary microbiota are functionally linked to the development and/or progression of PBC, remain to be resolved.

Dysbiosis has been extensively associated with the pathogenesis of IBD [90,91]. Thus, as PSC is frequently accompanied by IBD [56,57], changes in the microbiota are presumably also involved in the pathogenesis of PSC. In this context, it has been speculated that a putative gut-derived microbial trigger reaches the biliary epithelium via the leaky, inflamed intestinal epithelium, and the enterohepatic circulation [92]. Indeed, an experimentally-induced expansion of bacteria in the small bowel of rats perpetuated hepatobiliary inflammation resembling histological and cholangiographic features of PSC [93]. The application of a peptidoglycan-degrading enzyme improves biliary pathology in these rats, suggesting that microbe-associated molecular patterns are indeed involved in the induction of biliary disease [94]. Clinical studies describing a stabilization of liver enzymes upon antibiotic treatment further support the hypothesis that microbial triggers might be involved in the induction and/or progression of PSC [92]. In addition, alterations in the intestinal microbiota have been described in this patient cohort. For example, the relative abundance of Clostridiales II and the overall bacterial diversity is lower in PSC patients compared to UC patients (without concomitant PSC) and control individuals [95]. Interestingly, it has been suggested in this context that PSC-dependent dysbiosis is distinct and independent from the dysbiosis observed in IBD [96,97]. Furthermore, infections can complicate the course of disease. Thus, it has been reported that persistent biliary candidiasis is associated with a markedly reduced transplantation-free survival of PSC patients [98].

A recent report links a dysfunctional fucosyltransferase-2 (FUT2) to PSC [87] and Crohn disease (CD) [99], and the FUT2 genotype to the altered composition of the microbiota in the intestine and bile [87,99]. A genetic polymorphism within FUT2 alters the fucosylation (a form of glycosylation) of proteins which are shed into the intestinal [100] and biliary lumen [87]. Fucosylated proteins are known to influence metabolic pathways of intestinal commensals. Thus, they reduce (for example) the expression of bacterial virulence genes [100], and an increased abundance of Firmicutes as well as relatively lower levels of Proteobacteria and an overall reduced species richness in the bile have been associated with dysfunctional FUT2 [87]. Altogether, although compelling evidence for specific microbes associated with PSC is still lacking, these examples strongly suggest that microbial triggers influence PSC progression and that the microbiota can induce clinical complications in PSC patients.

Experimental evidence for the association of microbes with the pathogenesis of PSC is provided by additional studies. The (auto-)antibodies detected in PSC patients include atypical perinuclear antineutrophil cytoplasmic antibodies (p-ANCAs). p-ANCAs bind to the autoantigen β-tubulin isotype 5 (TBB-5) and its bacterial homologue FtsZ, which is ubiquitously expressed among the commensal microbiota [101]. p-ANCA, anti-TBB-5, and anti-FtsZ antibodies could only be detected in IL-10-deficient mice kept under single pathogen-free, but not germ-free condition [101]. Furthermore, the attachment of autoantibodies to biliary epithelial cells triggered an upregulation of toll-like receptor (TLR) expression, which might sensitize the biliary tract to microbial signals [102]. Thus, microbial triggers likely contribute to the formation and pathogenicity of these auto-antibodies.

However, the microbiota might also protect from PSC. In this context, it has been recently shown that fibrosis, ductular reaction, and ductopenia are significantly more severe in germ-free (GF) multidrug resistant 2 knockout (mdr2−/−) mice than in conventionally housed animals [103]. In this context, it is interesting to note that germ-free animals retain a global pool of only primary bile acids [104].
5. Conclusions

There exists compelling evidence that microbial agents and/or changes in the intestinal/biliary microbiota are involved in the pathogenesis of PBC and PSC. Thus, the application of antibiotics might be a novel and alternative therapeutic option for the treatment of these devastating diseases. Indeed, the application of antibiotics such as minocycline, metronidazole, or vancomycin has been reported to improve liver biochemistry and clinical symptoms of PSC patients, whereas the effects on Mayo risk scores and liver histology were less significant [92,105–111]. However, as antibiotics [112,113] are not species-specific, and both diseases are associated with alterations in the composition of the microbiota, the choice of the antibiotic substance, the duration of the use, the bile-permeability, and the availability have to be carefully considered, especially with respect to the fact that many of the microbial species and their function for the maintenance of immune tolerance have not yet been elucidated. Thus, antibiotic therapy appears to be promising. However, a long-term antibiotic can be associated with several adverse effects [114–116], including the perturbation of the resident microflora, the selection and spread of resistant microorganisms, and the development of other pathologies, such as diarrhea, colitis, sepsis, inflammatory bowel disease, obesity, and allergies [117–129]. As pathogenic bacteria might use the biliary tree as route for an ascending infection, and as ursodeoxycholic acid (UCDA, one of the secondary bile acids) is the only FDA-approved drug currently available for the treatment of PBC, its mechanism of action might include anti-microbial effects, as recently shown for Clostridium difficile infections [130] and/or the correction of alterations within the composition of the intestinal and/or biliary microbiota [131,132]. In order to address these pending questions, clinical studies must be initiated, and the therapeutic regimen carefully considered in order to identify therapeutic targets and approaches that can be used to guide the development of effective therapies for PBC and PSC, but also allows the identification of common targets in immune-mediated disease for clinical intervention in the future.

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