The "gut microbiota" hypothesis in primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a rare, immune-related disease characterized by chronic biliary inflammation and fibrosis of the intra and/or extra-hepatic biliary tree, leading to end-stage liver disease and biliary cancer. No medical therapies have demonstrated impact on the overall survival and liver transplantation (LT) is the only curative therapy (1). PSC is a complex condition characterized by the interplay between genetic predisposition and still unknown environmental factors. A better understanding of the disease etiopathogenesis would allow the development of specific therapies. The gut microbiota has recently evolved as a new important player in the pathophysiology of many intestinal and extraintestinal diseases, such as inflammatory bowel diseases (IBD), diabetes, obesity. It is to note that trials in PSC engaged antibiotics, both metronidazole and vancomycin, have shown a reduction in the alkaline phosphatase (ALP) (2,3). These data might suggest that manipulation of the gut microbiota could potentially influence the disease process in PSC.

In a recently published paper on *Gut*, Sabino *et al*. have investigated the intestinal microbiota composition in patients with PSC and have proposed that PSC has a characteristic microbial signature which is independent from IBD (4). In their study, a total of 175 individuals, divided in four different cohorts of patients were evaluated: patients with PSC only (n=18), PSC and IBD (n=48), IBD only (n=43), and healthy controls (HC) (n=66). Data about therapy in the last 30 days [in particular the use of antibiotics, probiotics, ursodeoxycholic acid (UDCA), immunosuppressors such as corticosteroids and anti-TNF], diet, living style, and disease conditions (stable, cirrhotic and liver transplanted patients) were collected. From each subject, fecal samples were collected, DNA were extracted and quantified, and microbiota analysis were performed in order to assignment a taxonomic sequencing 16S RNA genes (4). First of all, this study showed that the overall composition of the fecal microbiota was significantly different in patients compared to HC, with that from patients affected by PSC and PSC with concomitant IBD were different compared to that from the patients with only IBD. In particular, patients with PSC have a reduced microbiota with *Bacteroides* overrepresented and *Firmicutes* underrepresented compared to HC. In addition, it was found a consistent signature of four genera—*Enterococcus*, *Fusobacterium*, *Lactobacillus* and *Streptococcus*—which were overrepresented in both subgroups of PSC (PSC with and without IBD) compared to HC. Also *Streptococcus* genus was significantly increased in PSC and PSC with IBD patients, but its effect disappeared after taking into account antibiotic use. These results were independent of the treatment with antibiotic or UDCA, sex, smoking and cirrhosis or LT. *Enterococcus* was positively correlated with elevated ALP levels, but this correlation disappeared in the multivariate analysis. In addition, three different operational taxonomic unit (OTU) were assigned to the genus *Enterococcus*; one of these, OTU1, was significantly

associated with PSC, regardless of the subgroups, and correlated with ALP, although not confirmed in the multivariate analysis.

These results are consistent with the recent work of Kummen and colleagues who described a reduced bacterial diversity in PSC, regardless of the presence of IBD (5). In another study performed in a pediatric population of PSC and ulcerative colitis (UC) a lower species richness and abundance of *Enterococcus* (*E. faecalis* especially), *Streptococcus* (with prevalence of *S. parasanguinis*) and *Veillonella* species were found (6).

The big challenge to clarify is still whether these changes represent the trigger of PSC or are only a consequence of this liver disease, for example deriving from an alteration of the bile pool. Also, it is still unclear whether fecal microbiota are entirely representative of communities of mucosa-associated bacteria, which might uniquely interact with immune and epithelial cells.

An imbalanced intestinal microbiota characterized by an increased proportion of pro-inflammatory microorganisms and a decreased proportion of anti-inflammatory microorganisms, has been repeatedly observed in patients with IBD and is now well recognized as a key factor in the gut inflammatory processes. On the contrary, little data is available on the link between cholestasis and microbiota. It has been recently reported that a multidrug resistance 2 knockout ($mdr^{-/-}$) mouse model, a well-established animal model of PSC, shows higher serum markers of cholestasis and more advanced histological damage, such as increased liver fibrosis, ductular reaction, and ductopenia, when raised in a germ-free environment (7). The gut microbiota is essential for bile acid (BA) metabolism and regulates both the levels of primary BA synthesis, through modulation of the nuclear receptor, farnesoid X receptor, as well as production of secondary BA, such as deoxycholic acid, that are absent in germ-free mice (7). The absence of commensal microbial metabolites such as secondary BA with their anti-inflammatory properties might, in part, explains the link between gut microbiota and the liver.

A 'leaky gut' hypothesis has been proposed, suggesting that bowel disease and disruption of bowel permeability may eventually lead to microbial infection of bile, and subsequently causing cholangiocytes to activate a response that leads to inflammation and fibrosis within the liver. Considering that *E. faecalis* has already been associated with impaired intestinal permeability, it is to note that Sabino *et al*. observed an overrepresentation of the genus *Enterococcus* in fecal samples (4). In particular, gelatinase, a metalloprotease produced by *E. faecalis*, has been shown to alter the epithelial barrier, resulting in higher susceptibility to intestinal inflammation. The impairment of the epithelial barrier might allow bacterial translocation and bile colonization. Interestingly, *E. faecalis* and *E. faecium* have been the most frequently isolated species in bile in patients with PSC with dominant strictures (8,9).

High diversity of the intestinal microbiota is known to be a driving force for the evolution of the immune system, allowing the host to accommodate antigens and self-antigens. This ties in well with the 'gut lymphocyte homing' hypothesis in PSC which proposes that T cells are abnormally activated in the gut, with an erroneous recruitment to the liver, and a consequent triggering of hepatobiliary inflammation and fibrosis (10,11).

Most of the studies on microbiota are affects by a number of limits: first, they assess the use of drugs in a short preceding period, but do not consider the long-lasting effect of pharmacological agents on the microbiota. Second, the often neglect the dietary history, although is a key factor in the development of each individual microbiota. Unfortunately, while adjusting for structured diet approaches such as vegetarianism or gluten-free diet is feasible, there are no standardized methods to adjust for a detailed dietary history. Finally, the scenario is even more complex since recent evidences suggest that other factors such as the type of delivery (vaginal versus cesarean) and breast-feeding *vs.* formula-feeding affects the development of the intestinal microbiota, and this has been associated with chronic inflammatory conditions such as IBD (12-14). It is warranted that these factors should therefore be explored in future studies looking at the microbiota in PSC.

The study by Sabino and colleagues (4) provides a rationale for further studies on the microbiota in PSC with the aim to better understand its mechanisms and contribution to the disease, and to develop strategies to modulate the microbiota to treat or prevent disease. Ideally, in the future it may even be possible to use the microbiota to detect gut-related diseases before conventional diagnostics can.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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