



Mucosa-associated microbiota alterations in primary sclerosing cholangitis (PSC) before and after liver transplantation – who is calling the shots?

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Primary sclerosing cholangitis (PSC) is an immune-related chronic cholangiopathy associated with high rates of progression to liver cirrhosis and the need for liver transplantation. Since PSC is frequently associated with inflammatory bowel disease (IBD), several studies have investigated the role of the gut-liver axis in PSC and emerging evidence indicates that gut and bile microbiota are associated with the onset and progression of PSC [reviewed in (1)]. Interestingly, data from several reports have demonstrated that PSC-associated dysbiosis is not linked to the presence of IBD, suggesting that it is a result of progressive liver disease rather than gut dysfunction (2). Several studies on different etiologies of chronic liver disease such as non-alcoholic fatty liver disease (NAFLD) have shown that advanced liver disease is associated with reduced microbial diversity and an altered microbiota composition compared to mild or moderate disease, supporting the assumption that progressive liver disease drives gut microbial dysbiosis (3,4). Nevertheless, to what extent the alterations of the microbiota are the cause or the result of chronic liver disease is still an unresolved question. The causative role of dysbiosis in disease progression has been studied experimentally before. Specifically, the role of *Klebsiella* has been investigated in murine models and has

been shown to promote inflammation and hepatobiliary injury in PSC (5). While these data suggest that at least some perturbations of the microbiota are linked to the progression of the disease, it remains an open question whether PSC-associated liver injury promotes the changes in the microbiota and whether normalization of liver function reverts microbiota perturbations. Although liver transplantation can be considered as a curative treatment for patients with PSC, about 25% will develop recurrent disease. Investigation of the microbiota in PSC patients who underwent liver transplantation thus appears to be an attractive opportunity to explore the relationship between hepatobiliary injury and the microbiota and may provide insights into the mechanisms that promote the recurrence of PSC.

In their recently published study, Hole *et al.* (6) addressed these questions and analyzed the microbiota of 135 PSC patients, 51 of which had undergone PSC liver transplantation (PSC-LT), with 40 healthy patients serving as controls (HC). Instead of the fecal samples used by most previous studies that explored the microbiota of PSC patients, the authors chose to investigate mucosal samples obtained during colonoscopy, which were analyzed by 16sDNA seq. Several studies have suggested that mucosal

microbiota analysis may provide more stable results than fecal samples (7), although it is not clear whether this also applies to PSC. Mucosal sampling offers additional advantages, as it measures perturbations in different anatomical sites and could also be done retrospectively in cohorts for which biopsies, but not stool samples are available.

In congruence with previous studies that used fecal microbiota analysis, Hole and colleagues found reduced alpha diversity in patients with PSC and PSC-LT compared to HC. Principal coordinate analysis revealed a clear distinction between HC and PSC, while the difference between PSC and PSC-LT was less clear. Proteobacteria expansion is frequently considered an indication of dysbiosis. Indeed PSC, particularly PSC-LT, showed a significant increase in Proteobacteria. The expansion of Proteobacteria was associated with a loss of short-chain fatty acid producers, which is in accordance with the concept that perturbations of colonic homeostasis drive increased colonic oxygenation, loss of obligate anaerobes and expansion of Proteobacteria (8). In congruence with previous reports, most of these alterations were not linked to a diagnosis of IBD.

Together, these data suggest that PSC-specific dysbiosis is stable and is neither driven by colitis nor can it be normalized upon recovery of liver function after liver transplantation. This suggests that PSC-associated dysbiosis is either independent of liver disease or that it is driven by liver disease but remains stable and cannot be reverted after recovery of normal liver function.

Since the expansion of Proteobacteria may not only be associated with PSC but also promote disease progression—as shown for *Klebsiella* in experimental studies—the authors specifically explored the occurrence of *Klebsiella* in mucosal samples. Indeed, they found *Klebsiella* to be more abundant in PSC samples compared to HCs. Moreover, their data indicate that the abundance of mucosal *Klebsiella* is linked to shorter transplant-free survival in PSC. Finally, they also tested for a link between *Klebsiella* and the occurrence of recurrent PSC (re-PSC). Indeed, they found a higher proportion of *Klebsiella* in patients with re-PSC after LT compared to those without, although the data were not statistically significant due to the low patient numbers in their cohorts. Moreover, the presence of *Klebsiella* was linked to a shorter time to onset of re-PSC after LT.

The study provides important new insights into the role of the microbiota in PSC: firstly, the data confirm the dysbiosis features of PSC microbiota in mucosal samples. Secondly, the findings imply that the microbiota perturbations in PSC are stable and cannot be normalized

by transplantation. Therefore, additional strategies to target the microbiota in PSC patients are required. Thirdly, a role of *Klebsiella* as a driver of disease progression and re-PSC is suggested and therefore should be further investigated. Indeed, a recent report demonstrated that phage therapy targeting *Klebsiella* in murine models of PSC reduced liver inflammation and disease severity (9).

It should be noted that the study has potential limitations that may have influenced the reported findings. Firstly, there is a lack of information on diet and the use of antibiotics, probiotics, and proton pump inhibitors, all of which have a notable impact on the composition and function of the gut microbiota. Secondly, the possible effects of immunosuppressants in the PSC-LT group have not been considered. A recent study observed that the gut microbiome of liver and renal transplant recipients did not revert to a state comparable to that of controls from the general population (10). Instead, it was characterized by reduced microbial diversity independently from the etiology of liver and renal disease, a gain of pathogens at the expense of commensal bacteria, a decreased abundance of important metabolic pathways, and an increase in virulence factors and antibiotic resistance genes. Immunosuppressants were the single most important factor for the observed gut dysbiosis, which was in turn associated with a reduced likelihood of recipient survival (10). These observations and their reported independence from the etiology of liver disease both underscore the impact of immunosuppressive therapy on the gut microbiome and may explain why dysbiosis persists even when the underlying liver disease has been resolved by transplantation.

In conclusion, the study provides important information on key knowledge gaps. The reported findings now need to be validated in prospective, longitudinal studies that consider the mentioned limitations. Comparing the gut microbiota pre- and post-transplantation in the same patients could help to identify the mechanisms responsible for PSC recurrence after transplantation. The parallel examination of mucosal and fecal samples could, in case of comparable results, enable the development of simple non-invasive stool tests that can reliably predict PSC recurrence after liver transplantation.

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Footnote

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