PSC: *P*rotect and *S*erve with *C*olitis: does it help the liver to have severe ulcerative colitis?

Christian Rust, Stephan Brand

Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic disease of unknown aetiology affecting the biliary tree. It is characterised by bile duct inflammation and fibrosis, and in many patients it progresses to biliary cirrhosis and hepatic failure necessitating liver transplantation. A unique feature of PSC is its strong association with inflammatory bowel disease (IBD). In fact, at least 70% of patients with PSC also suffer from IBD, most commonly ulcerative colitis (UC). Conversely, only 2.5–7.5% of patients with IBD will develop PSC. Although this association has been known since 1965,[1] the underlying pathophysiology is still unknown. Despite this lack of fundamental information, hepatologists in clinical day-to-day business often note that patients with PSC are seldom troubled by severe UC. Are these just individual observations or does a common scheme exist?

Surprisingly, there are only a few studies addressing this issue. Patients with PSC with IBD seem to have a higher prevalence of pancolitis with rectal sparing and back-wash ileitis.[2] In this study, a lower rate of colectomies was noted in patients with PSC/UC as compared with patients with UC, suggesting a milder course of colitis in the PSC/UC group. Indeed, UC may have a long subclinical course in patients with PSC, as shown in a small Swedish cohort.[3] Two case–control studies also suggest that UC runs a milder course in patients with PSC than in those without this liver disease.[4 5] However, a possible association between the severity of PSC and the severity of UC has not been studied so far.

In their paper published in this issue of *Gut*, Marelli and co-workers (***see page 1224***) fill this gap with a single-centre study following 96 patients with PSC/UC over a long median follow-up period of 12 years.[6] These patients were divided into two groups according to PSC disease severity. This distinction was made using the need for liver transplantation (LT) during the follow-up period as a single, robust discriminatory parameter. Patients requiring LT (indicative of a clinically progressive PSC) had significantly less UC activity than those without LT. Moreover, the LT group needed fewer steroids or azathioprine for UC and had histologically significantly milder disease. Of note, none of the LT patients developed high grade dysplasia or colorectal cancer compared with 15% in the group without LT, although a bias might exist since the patients in the LT group were significantly younger. Thus, an inverse relationship between PSC and UC was revealed: mild UC associated with more severe PSC and, conversely, active UC associated with less progressive PSC. How can these interesting results be explained?

Again, little is known to enable this question to be answered. It would be interesting to know if IBD activity changes after the diseased liver is removed by LT. According to the data of Marelli *et al*, UC activity should worsen, although the situation after LT is more complex. Several studies showed more exacerbations of IBD after LT despite immunosuppressive maintenance treatment which has a beneficial effect on UC. This trend was also confirmed in the most recent study addressing this problem.[7] Fifty-nine patients with PSC were followed for up to 68 months after LT, and the course of IBD either remained stable or worsened. Interestingly, 29% of patients without a pretransplant diagnosis of IBD developed de novo disease after LT, which is also consistent with the results of Marelli *et al*.[6]

The underlying mechanisms cannot be explained satisfactorily at the moment, but some speculations are possible. Immune mechanisms play an important role in the pathogenesis of both PSC and UC. A number of associations have been made with HLA (human leucocyte antigen) haplotypes as well as non-HLA genes in patients with PSC, supporting an autoreactive component in PSC pathogenesis.[8] So far, only five of 47 established UC risk loci have also been replicated in PSC, suggesting a limited genetic overlap between both diseases.[9–12] Among these shared risk loci, *IL2/IL21*, *MST1* and *CARD9* represent interesting candidate genes for PSC and UC.

Interleukin 2 (IL-2) and IL-21 are important mediators of T cell development and seem to have opposing functions in immunity, with IL-21 predominantly mediating T helper 17 (Th17) cell-induced autoimmunity, while IL-2 has protective functions. For example, *Il2ra−/−* mice spontaneously develop both intestinal and biliary inflammation.[13] Defective IL-2 expression has also been shown in liver-derived T cells from patients with PSC.[14] Given the overlapping expression of endothelial adhesion molecules and tissue-specific chemokines between the liver and the intestine,[15] Marelli *et al* suggest that severe PSC with decreased liver function may also depress T cell function and therefore prevent T cell-mediated intestinal inflammation.[6]

Given the limited shared genetic background of PSC and UC, other factors such as bacterial antigens have been suggested to contribute to the pathogenesis of these diseases. Many pathogens affect the intestine as well as the liver (and the biliary tract). It has been hypothesised that colonic bacteria enter the portal circulation through a leaky mucosa in IBD, thereby causing PSC.[16] Bacterial antigens may act as molecular mimics in genetically susceptible people and cause an immune reaction responsible for initiating PSC. However, this does not explain why there are fewer patients with PSC with Crohn's colitis, which is characterised by transmural inflammation, as compared with UC in which inflammation is limited mostly to the mucosa. There is ample evidence since the 1970s that cell-mediated and humoral immunity is impaired in patients with liver cirrhosis.[17] So maybe it is the other way around: in PSC-associated liver cirrhosis the immunological attack against the colonic mucosa responsible for UC is blunted, resulting in less active colonic disease. In line with this hypothesis, re-establishment of the liver-associated immune system by LT could lead to more active UC despite the use of immune-suppressive drugs as has been shown.[7]

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In conclusion, the paper by Marelli and co-workers provides important clinical insight into the interaction of PSC and UC. Since this was a single-centre study, it is worthwhile for these findings to be reproduced by others to exclude a potential bias. If reproduced, future research should be directed to unravel the underlying mechanisms, which should help to understand not only the interaction between UC and PSC but also the still enigmatic pathophysiology of PSC itself.

Competing interests None.

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Benefits of bariatric surgery: an issue of microbial—host metabolism interactions?

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Obesity and type 2 diabetes are becoming worldwide epidemics. In this regard, the literature provides evidence that low-grade inflammation contributes to the onset of the metabolic disorders associated with overweight and obesity (insulin resistance, type 2 diabetes, cardiovascular diseases).[1] A considerable number of factors have been associated with the development of obesity, including the gut microbiota. The novel concept, that we defined as 'MicrObesity' (Microbes and Obesity), is devoted to delineating the impact of dysbiosis (changes in gut microbiota composition and/or activity) and its implications on host metabolism and energy storage.[2] Although the exact composition of the gut microbiota is not known, advances in metagenomic and metabonomic technologies have recently begun to unravel our microbial partners including the symbiotic complexity of the host—gut microbiota interactions, reflected by a specific chemical signature in the different biofluids.[3]

Over the last years, bariatric surgical approaches (eg, Roux-en-Y gastric bypass (RYGB) surgery) have provided interesting results, not only in achieving and maintaining appropriate weight loss, but most importantly by the resolution of type 2 diabetes independently of weight changes.[4] Although the modulation of gut peptides (glucagon-like peptide-1 and peptide YY (PYY)) has been shown to contribute to the improvement of diabetes and appetite sensations, these specific modifications do not explain per se all the metabolic changes associated with these surgical interventions.

In their paper published in this issue of *Gut* (***see page 1214***), Li *et al* have characterised the metabolic impact of RYGB in rats, through a ^{1}H nuclear magnetic resonance (^{1}H NMR) spectroscopy-based metabonomic approach, in combination with culture-independent technology (454 pyrosequencing) to characterise the gut microbiota.[5] Among the key findings, the authors have demonstrated an important increase in Proteobacteria (52-fold) and a fall in levels of Firmicutes (4.5-fold). Although the increase in Proteobacteria (γ-proteobacteria) has been reported previously in obese human subjects undergoing RYGB surgery,[6] this work further demonstrates that the main contributor to this change was *Enterobacter hormaechei* which increased by ~200- and 43-fold at weeks 2 and 8 post-RYGB surgery. Importantly, the study of Li *et al* was performed in non-obese rats. One would expect to find major differences between the lean and obese situation regarding the metabolic and the gut microbiota profiles following RYGB surgical intervention. However, a similar pattern (increase in Proteobacteria) was observed in the study of Zhang *et al*, performed in obese human subjects, and the experimental study of Liu *et al* performed in non-obese

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