ACKNOWLEDGEMENTS

Declaration of personal interests: None.

LINKED CONTENT

This article is linked to Rühlemann et al and Rühlemann and Franke papers. To view these articles, visit https://doi.org/10.1111/apt.15375 and https://doi.org/10.1111/apt.15434.

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DOI: 10.1111/apt.15434

Editorial: gut microbial profile associated with primary sclerosing cholangitis—what is new and how do we progress from here? Authors' reply

We thank Drs Quraishi and Shaheen for their comments on our study[1,2] and especially for raising the central question: How do we progress from here? We agree that further research is necessary to proceed from exploratory findings of an intestinal community that is distinctly changed in primary sclerosing cholangitis (PSC) patients of different ethnic origins to truly causal relationships between microbiota and disease.

Besides their suggestions, we think there is high potential in mechanistic insights gained from analyses based on shotgun and metabolomics data from faecal samples. Especially, longitudinal studies in combination with additional layers of omics data have shown exciting results in IBD[3] as reported by Curtis Huttenhower's group in the integrative Human Microbiome Project.[4] Following 132 study probands over the course of 1 year, they were not only

able to identify members of the microbial community that are probably linked to disease, but were also able to connect a subgroup of IBD patients with a dysbiotic state to reduced amounts of short-chain fatty acids and increased levels of a specific set of bile acids. Such longitudinal and higher-resolution analysis approaches may be able to bridge the gap of the evident differences in microbial communities across geographic regions and move emphasis towards a shared mechanistic or metabolic impact of the microbial communities on PSC. This study also shows that longitudinal sampling can serve as an alternative approach to the general notion that only larger sample sizes matter (increasing statistical power and robustness of results).

Nakamoto *et al*[5] recently revealed that strain-level resolution matters in microbiome analyses. In brief, they identified PSC-specific *Klebsiella pneumoniae* strains that disrupt the intestinal epithelial barrier to initiate bacterial translocation and liver inflammatory responses. Future studies should try to validate this finding and evaluate whether removal of these gut pathobionts, for example with antibiotics or bacteriophage cocktails, may improve or even cure disease. Nakamoto, pointing to an individual pathogen, clearly challenges the current hypothesis of a disease-relevant dysbiosis. Again, high-resolution and longitudinal shotgun metagenomics may reveal further gut pathobionts to be examined in more mechanistic studies.

Further potential, which is insufficiently covered by shotgun metagenomic analysis and has only recently been shifted into focus, lies in the often neglected non-bacterial members of the intestinal community: archaea and fungi. The study of Lemoinne and colleagues showed for the first time that a fungus—*Exophiala*—is associated with bacterial dysbiosis in PSC and leverages the findings of formerly bacterial-only to a trans-kingdom dysbiosis in PSC.[6] Recently it was highlighted that previous investigations of human-associated archaea offered a rather biased picture of archaeal diversity and new approaches for investigating this kingdom were proposed,[7] rendering archaea with its potential immunologic implication[8] amenable to analysis in disease context.

While our 16S rRNA study provides further evidence along the line of previously published articles that the intestinal microbiota plays a role in PSC aetiology, it also emphasises that in-depth and longitudinal multi-level analyses in PSC are needed to elucidate potential targets for mechanistic and intervention studies.

LINKED CONTENT

This article is linked to Rühlemann et al and Quraishi and Shaheen papers. To view these articles, visit https://doi.org/10.1111/apt.15375 and https://doi.org/10.1111/apt.15424.

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