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Commentary

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Evidence challenging the causal role of gut microbiota in inflammatory bowel diseases

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Recently, Bourgonje *et al.* [1] investigated the antibody epitope repertoire in patients with inflammatory bowel diseases (IBD) [1]. Using the high-throughput phage-display immunoprecipitation sequencing (PhIP-Seq) method, they made several significant findings, including elevated antibody reactivities against bacterial flagellins in patients with Crohn's disease (CD) and the effectiveness of the antibody epitope pattern in differentiating between CD/ulcerative colitis and healthy controls [1].

It is surprising that many peptide epitopes from *Roseburia* flagellin were highly over-represented in patients with CD, which contrasts with the result of our recent meta-analysis indicating a decreased level of this bacterium in CD [2]. Furthermore, the decreased abundance of *Roseburia* in pre-CD healthy individuals has been reported to be associated with the onset of CD [3]. In line with this disparity, Bourgonje *et al.* [1] found no significant association between the bacterial epitope repertoire and the gut microbial composition in patients with CD. The authors provided several explanations for the lack of association, including the insufficient coverage of the phage library used in their study [1]. Given that each individual harbors thousands of bacterial species, the authors estimated that their phage library covers ~10% of the bacterial epitopes within the microbiota [1]. In fact, based on rRNA sequencing data, it is estimated that the collective human gut microbiota consists of ≥1,800 genera and 15,000–36,000 species of bacteria [4]. Hence, the phage library might only cover a mere 1% of the bacterial epitopes of an average microbiota. This suggests that the PhIP-Seq study is far from comprehensive in capturing the entire microbial epitope repertoire in IBD. Therefore, future studies with a larger coverage of the epitope repertoire are needed for better understanding of the inflammatory targets in IBD.

However, with a phage library encoding 244,000 peptides covering 28,668 bacterial proteins, the PhIP-Seq study provides compelling evidence for the lack of association between the microbial composition and the immune response targeting the microbiota in individuals with IBD [1]. Notably, several other studies conducted by different research groups have also reached similar conclusions. In terms of humoral immunity, it has been observed that antibodies against *Escherichia* [5], but not the abundances of *Escherichia* [3], are associated with CD onset. With regard to cellular immunity, Bacteroidetes TonB-dependent receptors constitute a hotspot for both pro-inflammatory Th17 epitopes found in inflamed intestines and anti-inflammatory Treg epitopes present in healthy intestines [6]. Thus, the enhanced activation of both humoral and cellular immunity in IBD could be independent of changes in gut microbial composition.

In short, although the PhIP-Seq study by Bourgonje *et al.* cannot be considered a comprehensive study of the antibody epitope repertoire in patients with IBD due to the limited coverage of the phage library, it has provided compelling evidence supporting the lack of association between the microbial composition and the immune response targeting the microbiota in individuals with IBD. Despite the fact that the microbiota is the target of the immune responses in IBD and is required in the onset of the condition [7–10], the observations made by Bourgonje *et al.* [1] argue against a causal role of the gut microbiota in the development of IBD.

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Conflict of Interest

None declared.

References

1. Bourgonje AR, Andreu-Sanchez S, Vogl T *et al.* Phage-display immunoprecipitation sequencing of the antibody epitope repertoire in inflammatory bowel disease reveals distinct antibody signatures. *Immunity* 2023;**56**:1393–409.e6.
2. Gao S, Gao X, Zhu R *et al.* Microbial genes outperform species and SNVs as diagnostic markers for Crohn's disease on multicohort fecal metagenomes empowered by artificial intelligence. *Gut Microbes* 2023;**15**:2221428.
3. Raygoza Garay JA, Turpin W, Lee SH *et al.*; CCC GEM Project Research Consortium. Gut microbiome composition is associated with future onset of crohn's disease in healthy first-degree relatives. *Gastroenterology* 2023;**165**:670–81.
4. Frank DN, St Amand AL, Feldman RA *et al.* Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci USA* 2007;**104**:13780–5.
5. Lee SH, Turpin W, Espin-Garcia O *et al.*; Crohn's and Colitis Canada Genetics Environment Microbial Project Research Consortium. Anti-microbial antibody response is associated with future onset of Crohn's disease independent of biomarkers of altered gut barrier function, subclinical inflammation, and genetic risk. *Gastroenterology* 2021;**161**:1540–51.
6. Pedersen TK, Brown EM, Plichta DR *et al.* The CD4(+) T cell response to a commensal-derived epitope transitions from a tolerant to an inflammatory state in Crohn's disease. *Immunity* 2022;**55**:1909–23 e6.
7. Harper PH, Lee EC, Kettlewell MG *et al.* Role of the faecal stream in the maintenance of Crohn's colitis. *Gut* 1985;**26**:279–84.
8. Sadlack B, Merz H, Schorle H *et al.* Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. *Cell* 1993;**75**:253–61.
9. Sellon RK, Tonkonogy S, Schultz M *et al.* Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. *Infect Immun* 1998;**66**:5224–31.
10. Jensen SK, Pærregaard SI, Brandum EP *et al.* Rewiring host-microbe interactions and barrier function during gastrointestinal inflammation. *Gastroenterol Rep (Oxf)* 2022;**10**:goac008.