

## EDITORIAL

## Zooming in on Inflammatory Bowel Disease: Microbial and Proteomic Features Associated With IBD in Colonic Microenvironments



Inflammatory bowel disease (IBD) is a multifactorial chronic intestinal inflammatory disorder characterized both by genetic and environmental factors.<sup>1</sup> Among the latter, the microbiome recently emerged as one of the most promising avenues of research to understand the pathogenesis of IBD. Several studies have shown differences in microbiome composition and diversity in IBD patients compared with healthy controls.<sup>2,3</sup> Larger cohorts have allowed for further characterization of the gut microbiota in IBD patients, including assays that determine function and activity of the microbiome and thus provide better mechanistic insights.<sup>4–6</sup> Most of these studies, however, investigated microbial composition in stool or in the colonic mucosal surface, missing potentially important factors hidden in deeper layers of the colon. Furthermore, we still lack a good understanding of how the microbiome interacts with the host at the proteomic level. The September issue of *Cellular and Molecular Gastroenterology and Hepatology* presents 2 new exciting articles that highlight the importance of in situ microbiome structure in deep colonic layers and metaproteomic functional networks in the characterization of IBD.

Pedamallu et al<sup>7</sup> analyzed the microbiome structure in deep layers of the ileum obtained from Crohn's disease (CD) patients and compared it with IBD-free controls who had undergone surgery for right-sided colon cancer. The authors distinguished involved (diseased) and uninvolved areas using microscopy in samples from CD patients. Although CD patients and controls differed in bacterial composition at the phylum level (with a significant depletion of *Bacteroidetes* in patients), no such differences were observed between involved and uninvolved regions in the first group. It is possible, however, that some of the observed differences were caused by the administration of metronidazole and levofloxacin to CD patients during the course of the disease. Direct comparison of involved and uninvolved areas in patients found a statistically nonsignificant, but intriguing, enrichment of *Staphylococcus* and *Delftia* in the former. Interestingly, a *Staphylococcus aureus* pathogenicity island was detected in involved tissue from 2 patients, suggesting that enterotoxigenic strains could be partially responsible for localization of lesions in CD. Comparison of involved and IBD-free tissue also showed enrichment in *Mycobacterium* species in disease, particularly *Mycobacterium abscessus*.

Li et al<sup>8</sup> used metaproteomics (the set of host and microbial proteins found in a given environment) to characterize the mucosal–luminal interface in CD and

ulcerative colitis (UC) patients compared with healthy subjects. The authors collected mucosal lavages at 6 colonic regions from IBD and non-IBD subjects, and found that roughly one third of the proteins in the lavages were of bacterial origin, with nearly half of those being produced by *Bacteroidetes*. Primary component analysis identified intersubject variability as the major contributor to variance (57.5%) of the metaproteome, followed by disease (21.5%), and colonic region (15%). By using correlation network analysis, the authors identified mucosal protein modules with different functional activity and cellular origin. Three of these modules were linked to the colon, but 6 were related to disease. Further characterization of these modules identified some of their member proteins, among which several were associated with disease. These included  $\alpha$ -defensins such as human neutrophil peptide (increased in UC and CD), hepcidin and transferrin (enriched in UC patients), or human  $\beta$ -defensins (increased in CD). Bioinformatic analysis, immunoblotting, and immunohistochemical assays also suggested the spatial localization of different protein patterns as distributed in a microgeographic mosaic, with scales ranging from microns to millimeters. The authors thus hypothesized that the mucosal surface is heterogeneous, and consists of local mucosal functional networks with specific regions enriched in metabolic activities that provide a habitat for host responses contributing to disease states.

These results present compelling evidence of the nonhomogeneous nature of the intestinal mucosa and of how different regions of the colon harbor microenvironments colonized by different bacterial species that could determine disease state. The interaction of localized microbial communities and the host through specific proteomic networks can induce host responses that determine disease course, suggesting potential targets for therapeutic interventions. Given the high intersubject variability observed, future studies would benefit from longitudinal sampling in which each subject could serve as his or her own control, thereby improving power to detect features directly associated with disease or location. The low biomass of tissue samples is also an important technical hurdle in microbiome studies,<sup>9</sup> and standardized methods that improve their handling and processing would be a major advance. Improved methods for selectively enriching bacterial DNA and protein while reducing human contamination also will be critical tools as we improve our understanding of how microbes and microbial products contribute to IBD pathogenesis.

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### Conflicts of interest

The authors disclose no conflicts.

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