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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Tracking Dysbiosis Where It Matters

The study of the intestinal microbiota has come a long way from its niche existence in research on the intestinal flora, which relied on culturing bacteria to identify phyla in the 1950s. Today, even lay people talk about their gut microbes with conviction, if not authority, and probiotic nutritional supplements are a billion-dollar industry. In fact, *Cellular and Molecular Gastroenterology and Hepatology* recently published a review article addressing the question whether microbiota-based dietary intervention should be instituted for the treatment of inflammatory bowel disease.[1] An explosion in knowledge in this field came about when 16S rRNA gene sequencing became a cheap and experimentally easy method to determine and quantify bacterial phyla in stool samples. Analytical tools borrowed from ecology were introduced to describe bacterial communities, with high diversity often presumed although rarely proven to be beneficial to human health. Changes in the stool microbiota relative to healthy subjects, or dysbiosis, were reported to contribute to or even be causative of not only gastrointestinal disorders but many other diseases including type 2 diabetes, anxiety, or Alzheimer's disease,[2] and these studies quickly found their way into the lay press.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Maria Abreu's group from the University of Miami asks the question whether the analysis of the microbiome from stool samples or even whole colonic biopsies is the optimal way to assess its impact on inflammatory bowel disease, or whether it might be more informative to analyze the microbiota that are in contact with lamina propria phagocytes.[3] To this end, Dheer et al[3] isolated CD11b-positive phagocytes from biopsies of patients with Crohn's disease or ulcerative colitis. CD11b marks cells of the innate immune system such as macrophages, monocytes, and neutrophils which are the first responders to bacteria that invade the ileal or colonic epithelium. The authors reasoned that the phagocyte-associated bacteria would be a better reflection of the disease-relevant microbes than stool or whole mucosal specimens.

After fluorescent-activated cell sorting of phagocytes, bacteria were classified and quantified by using standard 16S rRNA high-throughput gene sequencing. As reported previously,[4] stool microbial composition differs significantly from that of whole mucosal biopsies. Notably, Dheer et al[3] also discovered substantial differences between the phagocyte-associated microbiota and those found in whole biopsy samples, the latter of which differed from sample to sample because of varying depth of biopsy and the degree of remaining adherent stool. Importantly, several of the phagocyte-associated phyla, such as *Prevotella* species, had been reported previously to promote Th-17 mediated mucosal inflammation.[5] Thus, this study suggests that selective invasion of the mucosa by inflammation-promoting bacteria could modify the immune response.

Another finding that demonstrates the granularity of this novel approach derived from the comparison of microbiota associated with inflamed and noninflamed tissue from ulcerative colitis and Crohn's disease patients. Although whole mucosal microbial analysis demonstrated more differences between the 2 diseases at noninflamed versus inflamed sites, as seen by others,[6] this was not the case when the phagocyte-associated microbiome was analyzed. Here the authors found numerous differences in phagocyte-associated microbe composition in inflamed tissue from ulcerative colitis or Crohn's disease patients. Thus, for the first time it appears that microbiota are different between the 2 diseases in the setting of inflammation.

In sum, Dheer et al[3] have moved the needle on our understanding of inflammatory bowel disease–associated dysbiosis by focusing on analysis of microbes likely to matter most in this context, that is, the bacteria that are interacting with the innate immune system. One caveat of the study is that their methodology does not distinguish between bacteria that are only attached to phagocytes from those that have already been engulfed. In addition, lacking from the study is a comparison with the phagocyte-associated microbiome from healthy individuals. Nevertheless, this work represents a major advance in the field and suggests that some conclusions from prior studies might need to be revisited.

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Conflicts of interest
The author discloses no conflicts.

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2352-345X
https://doi.org/10.1016/j.jcmgh.2019.11.015