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EDITORIAL

Disease-Associated Microbial Communities in Healthy Relatives: A Bacteria-Filled Crystal Ball?

The bacterial community within the gastrointestinal tract has been the subject of a great deal of investigation as well as a great deal of press. Numerous studies have shown that inflammatory bowel disease (IBD) is associated with an alteration in the ecological system within our gut,[1] and findings from mouse models suggest that inflammation-associated microbiota transplanted from human IBD patients can contribute actively to colitis.[2] Still, it is not clear whether dysbiosis is either necessary or sufficient as an initiating event—especially in human beings—or if in contrast only a microbiome that already has been shaped by the inflammatory state is able to contribute further to disease. If a dysbiosis is an instigator, then in principle it should be possible to detect this defect in otherwise healthy populations who are at increased risk for disease, such as healthy relatives of IBD patients.

In a new study published in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Jacobs et al[3] do exactly that. Performing a thorough analysis of fecal microbial profiles from 36 IBD patients in remission (26 with Crohn's disease and 10 with ulcerative colitis) and 54 healthy first-degree relatives, they showed that it is possible to identify an IBD-like intestinal microbiome in at-risk healthy individuals who do not have clinically detectable inflammation. In the study's data set, individuals could be clustered into either a disease-associated or a healthy microbial signature at both the operational taxonomic unit (OTU) and metabolomic levels. The IBD-associated microbial community type was a reduced-diversity signature compared with the healthy state, and included expansion of families such as Enterobacteriaceae and Prevotellaceae. The metabotype associated with IBD was enriched for taurine, tryptophan, and altered bile acids and metabolites similar to those shown previously to be altered with disease. Importantly, given the small number of patients included here, the investigators also used the much larger RISK data set of early onset IBD[4] to validate their diseased vs healthy genomic grouping.

The key finding of their report was the observation that the disease-linked OTU type and metabotype were present in a substantial subset of clinically healthy first-degree relatives. Some of the healthy relatives with an IBD-like microbial community had increased levels of fecal calprotectin, suggesting that they may be on the road to developing inflammation. Importantly, the majority of this group did not have high calprotectin levels, which is consistent with the idea that the microbial changes can come before even subclinical inflammation. Together, these observations raise the provocative possibility that, at least in some individuals, the IBD-associated OTU type represents a predisease or disease susceptibility state. At the very least, they show that dysbiosis can occur in at-risk individuals in the absence of obvious clinical symptoms. This advance has the promise of clinical utility—if necessary follow-up long-term studies show that healthy family members with the IBD-type microbial community are more likely to develop IBD, this signature could be used to stratify relative risk. Furthermore, although there have been substantive challenges with attempts at therapeutic microbial alteration (eg, fecal microbial transplant) in IBD, it may be the case that a predisease/high-susceptibility gut ecology that has not yet synergized with an ongoing inflammatory response will be more amenable to treatment.

The metabolomic data presented in this study are intriguing, although the direct causal links between the OTU type and metabotype and the role of this metabotype in instigating or prolonging disease are not yet known. For the most part, the investigators found that the OTU and metabolic types were well correlated. Interestingly, however, the taxonomy and metabotype were discordant in approximately 20% of the individuals studied. The discordant individuals were in both the healthy and IBD groups, which does not rule out a contributory role but suggests, at least at this level of analysis, that the metabotype described in the report is not an essential driver of disease.

Going forward, prospective longitudinal studies in an expanded and more diverse cohort will be essential to determine whether the microbial signatures described by Jacobs et al[3] are indeed markers for a predisease state. Furthermore, because evidence suggests that mucosa-adherent microbes may correlate more tightly with the disease state than fecal communities,[5] it would be interesting to see whether typing using these communities could provide even more sensitive measures of susceptibility. Overall, the presence of a distinct microbial community and metabolomic signature in the absence of symptoms is an important step toward understanding the sequence of IBD onset.

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