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EDITORIAL

Fusobacterium varium in Ulcerative Colitis: Is It Population-Based?

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Certain members of the *Fusobacterium* genus, notably *F. nucleatum*, *F. necrophorum*, and *F. varium* have recently gained notoriety as gastrointestinal pathogens; *F. nucleatum* in particular has been associated with appendicitis, Crohn's disease, and colorectal cancer [2]. *F. varium* was first associated with ulcerative colitis (UC) by Ohkusa et al. [3], who subsequently characterized bacteria isolated from inflamed mucosal biopsies of ten patients with active UC. Remarkably, half of the tested samples contained *F. varium*, which, when cultured, produced a butyrate-rich supernatant that induced experimental UC in mice [3]. The same group has subsequently demonstrated that *F. varium* can invade colonic epithelial cells and initiate a pro-inflammatory response [4]. Moreover, combination antibiotic therapy with proven in vitro effectiveness against *F. varium* reduced *F. varium* counts in active UC patients while improving clinical activity and endoscopic and histological scores, compared to a non-treated control group [5], and inducing a long-term remission-typical alteration of the intestinal microflora [6]. These preliminary data support an association between *F. varium* intestinal infection and UC disease activity.

In this issue of *Digestive Diseases and Sciences*, Tahara and colleagues use quantitative real-time polymerase chain reaction (qPCR) to report the prevalence of *Fusobacterium* spp. in colonic biopsy tissues obtained from 152 UC patients in a prevalence screen [1], building on the data reported by the Okhusa group. The use of qPCR rather than culture and terminal restriction fragment length polymorphism (T-RFLP) in a much larger cohort of patients stratified according to disease severity is technically and methodologically superior to procedures used in the prior studies. Building on findings demonstrating the emerging importance of *F. nucleatum* as a gut pathogen, Tahara et al. used PCR primers specific for this species in addition to primers designed to amplify diverse *Fusobacterium* species, termed "pan-*Fusobacterium* signatures" which were present in 54.6 % of the biopsy specimens tested, although only 6.3 % of positives were associated with *F. nucleatum*, suggesting that in this population at least, *F. nucleatum* was not significantly associated with disease. Although the primer sets of the Tahara et al. study were not specific for *F. varium*, searching for this organism in the same population in a future study is likely to yield important data.

In a number of recent studies, high-throughput sequencing methods were used to probe the microbial composition of gut-derived samples in inflammatory bowel disease, including UC [7–9]. Intriguingly, none of this work indicates that *Fusobacterium* spp. are particularly prevalent, or even present, in the samples studied. How can these findings be reconciled with the data discussed above? First, the potential pathogenic role of *F. varium* in UC has, to date, only been examined in Japanese patients, whereas most of the sequence-based analyses of UC have been performed on cohorts in other parts of Asia, as well as North America and Europe. Because of its unique history, Japan was mostly isolated from other countries until $\sim$ 150 years ago, which likely explained the observed differences in the gut microbiota of Japanese populations in comparison with populations from other countries [10, 11]. It is possible, then, that gut dysbiosis triggered by the recent Westernization of Japan, which is widely thought to be responsible for increasing rates of IBD there, could manifest as variations in microbial taxa among the world's peoples? Thus, the involvement of *Fusobacterium* (in particular *F. varium*) in

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UC may be specific to Japan. Secondly, members of the *Fusobacterium* genus are noted for the G+C contents of their genomes, which are particularly low (<35 %) [12]. Since there are limitations to the amplification of AT-rich DNA in shotgun sequencing strategies, it is therefore possible that the fusobacterial load is underestimated in sequence-based surveys of the gut microbiota.

Finally, since many *Fusobacterium* spp. typically associate with host epithelial tissues, they are not commonly easily detectable in stool [13]. Thus, it is important, as in the Tahara and Ohkusa studies described above, that mucosal biopsies (rather than stool samples) are used to assess the *Fusobacterium* load in a patient, or that specific enrichment methods are used on stool samples where mucosal biopsies are unavailable [14].

In summary, the highly interesting findings of the Japanese groups deserve further study. An important future direction will be to determine whether results similar to those reported by Tahara et al. can be obtained using mucosal biopsies from patient cohorts outside of Japan, in which case the use of targeted methods for fusobacterial detection, perhaps with higher species resolution, will be extremely valuable. Even if fusobacteria are found to be associated with only a minority of global cases of UC, the demonstrated benefits of antimicrobial therapy in such cases mean that for some UC patients diagnosis and treatment options might be increased substantially.

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