# Promote or Prevent? Gut Microbial Function and Immune Status May Determine the Effect of Fiber in Inflammatory Bowel Disease

**See "Unfermented β-fructan fibers fuel inflammation in select inflammatory bowel disease patients," by Armstrong HK, Bording-Jorgensen M, Santer DM, et al, on page 228.**

The benefit of dietary fiber in promoting human health has been long recognized and is largely based on the lower prevalence of Western diseases such as diabetes, heart disease, and colorectal cancer among populations that consume higher amounts of dietary fiber.[1–4] Although not well-understood, the protective effects of fiber had been previously attributed to faster transit time and stool size, which may facilitate the removal of toxic metabolic products.[5] However, recent studies show that microbial fermentation likely underlies the benefits of dietary fiber.[6,7] Gut microbiota harbor a diverse set of enzymes such as glycoside hydrolases and polysaccharide lyases that help to break down specific linkages in complex carbohydrates derived from host glycans or dietary fiber into simple sugars. The enzymes profile of these communities will likely determine the specific carbohydrates that can be fermented by an individual's gut microbiota. The resulting fermentation end-products, such as short chain fatty acids,[8] regulate important aspects of host physiology including metabolism, cell turnover, and the immune system. Hence, one would expect to see beneficial effects with fiber supplementation. However, human interventional studies show significant interindividual variability in responses to fiber as well as differences based on fiber type.[9] In this issue of *Gastroenterology*, Armstrong et al[10] systematically address the complexity that underlies differences in response to fiber by investigating the effects of different β-fructan fibers on barrier function and inflammation using a combination of human specimens, ex vivo culture of colonic biopsies, and cell culture models.

One of the challenges in the field is that carbohydrates that differ in chemical composition and size, resulting in varying potentials to undergo microbial fermentation along with nonfermentable components, such as lignin are all categorized as fiber. Armstrong et al[10] found that certain β-fructans such as fructo-oligosaccharide (FOS) and inulin, but not barley, maltodextrin, or starch, triggered a proinflammatory response in THP-1–derived macrophage cell lines and primary peripheral blood mononuclear cells from healthy donors as evidenced by increased release of IL-1β. This finding suggests that different carbohydrates classified as fiber can evoke different biologic responses. However, Armstrong et al[10] found the proinflammatory effect was not only dependent on the fiber type, but also on immune status of an individual and the fermentative capacity of their gut microbiota (Figure 1*A*).

The authors cultured colonic biopsies from pediatric patients with Crohn's disease and ulcerative colitis with both active and quiescent disease and from controls without inflammatory bowel disease (IBD). They found higher levels of $CD45^+$ cells in biopsies from patients with IBD. FOS significantly increased IL-1β secretion in colonic biopsies from patients with active IBD and, to a lesser extent, from those with quiescent disease, but decreased IL-1β secretion in biopsies from controls without IBD. The proinflammatory effect of FOS was mediated via the NLRP3 and TLR2 pathways. Thus, FOS can differentially affect immune responses based on the underlying immune cell population in the gut. Interestingly, the authors also found that the avoidance of FOS among pediatric patients with IBD correlated with a proinflammatory response to FOS, suggesting that FOS consumption during health may decrease the severity of inflammation subsequently. This observation raises additional questions about the mechanisms underlying the effect of distinct fibers on the gut–immune system in different states of health and disease.

Armstrong et al[10] assessed the effect of microbial fermentative capacity on the inflammatory response by exposing THP-1 cells to supernatants from colonic washes cultured in the presence or absence of FOS. They found the fermentative capacity of the gut microbiota as evidenced by levels of FOS and short chain fatty acids negatively correlated with the inflammatory response evoked by FOS. The dampened immune response was dependent on both a decrease in FOS as well as an increase in short chain fatty acids, suggesting potential complementary mechanisms underlying this effect. To complement their observations with findings in human subjects, these authors used samples from a clinical trial of adult patients with ulcerative colitis treated with β-fructans and found that symptom flares during β-fructan supplementation correlated with increased inflammatory cytokines in intestinal biopsy lysates.

The findings of Armstrong et al raise as many questions as they answer. In this study, the authors deconstructed the complexity of food by investigating individual carbohydrates with varying complexity. Authors found that select carbohydrates can affect immune function, but because these molecules were purified from chicory roots, the potential role of microbial contaminants that may copurify with β-fructans cannot be ruled out. Moving forward, it will be important to build back this complexity by combining different carbohydrates to better understand the impact of complex foods, as well as the modifications that occur with food preparation and cooking. Interventional studies[11] have shown that rapid

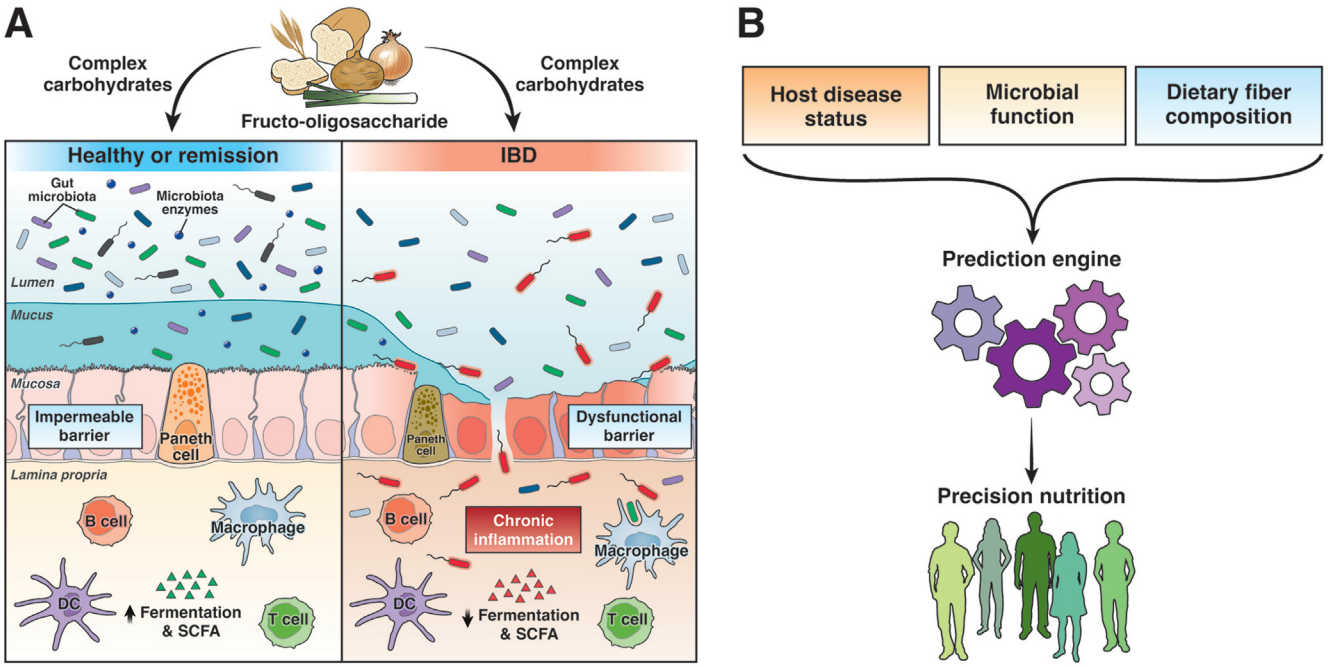


**Figure 1.** (*A*) Outline of factors described in the study and additional potential determinants of the effect of different fibers on host function. (*B*) Precision nutrition approach will require integrating the different host, microbial, and diet features. SCFA, short chain fatty acid.

shifts in the gut microbiota and associated changes in microbial metabolism occur with short-term dietary changes and that food-derived microbes can be detected in the distal gut. Single fiber effects do not occur in isolation. Indeed, other investigators have reported the benefits of combining fiber consumption with reduced protein intake for reducing colitis severity in animal models.[7]

Although the study focuses on mucosa-associated microbiota, it is potentially important to also assess the luminal microbiota to determine overall fermentative capacity in different segments of the gut (Figure 1*A*). Further, the study uses metagenomics to assess the functional capacity of the microbiome, but it is difficult to predict the phenotypic ability of bacteria to use specific carbohydrates based on metagenomic sequences alone, given that bacteria do not express all their genes in a given environment. In addition to promoting the growth of the specific microbes that use them, dietary carbohydrates can also promote other microbes that depend on the end-products of primary fermenters (cross-feeding). Hence, it is not surprising that, although functional differences were observed in the microbiota between FOS responders and nonresponders, these differences do not directly explain the differential capacity for FOS fermentation. Thus, it will be important to complement sequencing data with biochemical characterization to determine specific enzymatic activity in a microbial community which in turn provides a therapeutic target (Figure 1*A*). The acquisition of enzymes capable of digesting algae by the microbiome in Japanese individuals[12] highlights one potential pathway for introducing missing enzymatic capabilities into a microbial community.

The findings of Armstrong et al are compelling and have implications beyond IBD. Another recent study found specific foods (gluten, wheat, soy, milk) may evoke pain through local immune responses with mast cell activation in patients with irritable bowel syndrome.[13,14] It is plausible because the differential fermentative capacity of small intestinal microbiomes plays a role in determining food-evoked pain. The current study highlights the complexity of factors involved in an individual's response to fiber, such as the carbohydrate chemical structure, the enzyme repertoire of the gut microbiota, and host immune status. Although there are likely additional determinants, these observations help to explain the interindividual differences in response to fiber supplementation and underscore the need for precision nutrition approaches rather than the one-size-fits-all fiber supplementation strategy in disease states (Figure 1*B*). A broader approach of fiber supplementation may still be relevant in health, especially among populations with overall low fiber consumption.

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**Conflicts of interest**
The authors disclose the following: A.S. serves on Ardelyx Scientific Communications Advisory Board for irritable bowel syndrome with constipation. P.C.K. is an ad hoc consultant for Pendulum Therapeutics, IP Group Inc., and Intrinsic Medicine. P.C.K. holds the patent US20170042860A1 "Methods and materials for using *Ruminococcus gnavus* or *Clostridium sporogenes* to treat gastrointestinal disorders" for use of tryptamine producing bacteria to treat gastrointestinal disorders. Mayo Clinic and P.C.K. have a financial interest related to use of tryptamine-producing bacteria.

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**Most current article**


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# Shining a Light on Barrier Function

**See "Intestinal barrier healing is superior to endoscopic and histologic remission for predicting major adverse outcomes in inflammatory bowel disease: the prospective ERIca trial," by Rath T, Atreya R, Bodenschatz J, et al, on page 241.**

End points in clinical trials and treatment targets in practice are only as good as the outcomes they predict. The outcome that matters most to patients with ulcerative colitis (UC) or Crohn's disease (CD), short of a cure, is the relapse rate. Major adverse outcomes (MAO) such as steroid, biological, or immunosuppressant small molecule therapy, let alone hospitalization or surgery all stem from a relapse. It has become increasingly apparent that the deeper the depth of remission, the lower the risk of relapse, but some definitions of remission are easier to achieve than others (Figure 1). In the early 2000s, the concept of deep remission was introduced, meaning symptomatic remission and endoscopic mucosal healing.[1] Now, in the 2020s, the concepts of histoendoscopic mucosal improvement and histoendoscopic mucosal remission are gaining traction.[2–5] A meta-analysis of 17 trials in UC showed that the relapse rate after achieving a Mayo Endoscopic Subscore (MES) of 1 was associated with a 29% relapse rate in the following year, but just 14% when the MES was 0.[6] However, when there was histologic remission (absence of epithelial or lamina propria neutrophils on mucosal biopsy) as well as an MES of 0, the 12-month relapse rate was just 5%.[6] An iceberg analogy has been popular, with symptoms representing the visible berg above the surface and biochemical, endoscopic, and histopathologic activity representing the bulk of disease below the surface, with its proclivity to relapse.

Enter ERIca. The Erlangen Remission in IBD (ERIca) trial[7] studied 181 patients with either UC (n = 81) or CD (n = 100) in clinical remission, during follow-up for a mean of 25.0 ± 11.9 months for UC and 35 ± 6.9 months for CD. These 2–3 years are a material period in a life-long disease. The composite outcome of interest was the occurrence of MAO, including disease flares, inflammatory bowel disease–related hospitalization or surgery, and escalation of advanced therapies or steroids. This is a practical end point relevant to clinical practice. The MAO predictive value of endoscopy, histopathology and intestinal barrier integrity measured by confocal laser endomicroscopy (CLE) were