Probiotic Bifidobacterium species: potential beneficial effects in diarrheal disorders. Focus on “Probiotic Bifidobacterium species stimulate human SLC26A3 gene function and expression in intestinal epithelial cells”

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Diarrhea caused by enteric (bacterial/viral/parasitic) infections or diarrhea associated with inflammatory bowel disease represents a major health care burden worldwide (10). In addition, diarrhea associated with antibiotic administration in adults, as well as children, is a significant health care issue (1, 3). Diarrhea is also a common side effect of chemotherapeutic agents during cancer treatment (6). Antidiarrheal drugs generally have been shown to cause nausea, loss of appetite, and constipation, which often hinder treatment protocols (15). Diarrhea can be a consequence of the imbalance of water and ion absorption by epithelial cells of the gastrointestinal tract, ultimately leading to enhanced secretion and/or diminished absorption of fluid and electrolytes. Aberrant ion movement across epithelia can occur through a paracellular pathway via tight junctions or a transcellular pathway via membrane transporters such as Na+/K+-ATPase (1). Na+/H+-exchanger 3 (NHE3), Cl−/HCO3− exchanger isofrom 3, Cl−/HCO3− exchanger, and downregulated in adenoma (DRA), which can be dysregulated in diarrhea (10). Infectious pathogens can alter ion transporters directly or may induce electrolyte imbalance via increased inflammation or reduction in the absorptive capacity of the epithelial cells (12). Several studies of the functional implication of DRA in diarrheal disorders have been published (4, 7, 13).

A large and growing literature describes studies of the beneficial health effects of live microorganisms in treating gastrointestinal disorders. There are several trials with bacterial formulations of Bifidobacterium in conjunction with other species of probiotic strains to treat diarrheal symptoms, although strong mechanistic studies regarding the usability of individual species of Bifidobacterium by itself are lacking. Bifidobacterium belongs to the class of an aerobio, gram-positive bacteria that are part of the natural microbial flora of the gastrointestinal tract (5). This gap in understanding of the signaling mechanisms associated with the use of a particular probiotic strain poses challenges to the claims made by the food industry.

In this issue of American Journal of Physiology-Cell Physiology, Kumar et al. (11a) report that Bifidobacterium species might serve as a potential therapeutic approach for treating diarrhea arising from ulcerative colitis or enteric infections (2, 9). Consistent with previous findings in diarrheal diseases, the in vivo and in vitro studies of Kumar et al. provide strong evidence that enhanced expression of DRA (mediated by treatment with live and culture supernatants of Bifidobacterium, respectively) stimulates Cl−/HCO3− exchanger activity. The authors demonstrate that treatment of Caco-2 cells with supernatants from cultures of various Bifidobacterium species enhances Cl−/HCO3− exchange activity, with a concomitant increase in DRA mRNA and protein expression. Increased DRA mRNA transcription was experimentally blocked by actinomycin D, which resulted in abrogation of the effect of Bifidobacterium breve and Bifidobacterium infantis. Previous studies showed a preferential expression of DRA relative to that of putative anion transporter 1 (PAT-1) in the colonic region (8). Kumar et al. also studied the anion exchanger PAT-1 to determine its role in the stimulation of Cl−/HCO3− exchanger activity. Other studies showed that PAT-1 is refractory to regulation; consistent with such findings, Kumar et al. did not observe an effect of Bifidobacterium treatment on this gene. They also demonstrated the role of the ERK1/2 MAPK signaling pathway in the activation of DRA, thereby advancing the understanding of the potential mechanism of action of probiotic strains on DRA expression. Although treatment of diarrhea with a mixture of probiotic species has been reported (1), the study of Kumar et al. represents a significant advancement toward elucidation of the role of specific species of bacteria as potential probiotic/antidiarrheal agent. The proposed mechanism of action of Bifidobacterium species on the regulation of DRA expression is summarized in Fig. 1.

Although several different anion exchangers have been shown to participate in maintaining water and electrolyte balance, increasing evidence for the role of DRA in diarrhea underscores the importance of further studies of this transport protein. For example, DRA expression can be altered in diarrhea associated with infections and antibiotic treatment (3, 4, 7, 10). In addition, the DRA−/− mouse model has been used to characterize the role of DRA in diarrheal disorders (14). Mutations of the transporter slc26a3 (the gene encoding the DRA protein) result in aberrant electrolyte balance in congenital Cl− diarrhea (11). Probiotic treatment of gastrointestinal disorders with diarrheal symptoms is currently under study, including several clinical trials with formulations containing Lactobacillus species and Bifidobacterium species (6). Despite these studies, there are limited reports of the role of Bifidobacterium by itself and also the factors generated by this species that improve diarrheal symptoms. Thus it is important to study the mechanisms of action of possible soluble factors that are secreted from Bifidobacterium species and regulate the transporters involved in anion absorption in the gastrointestinal tract.
The study of Kumar et al. (11a) has a few minor limitations. The mouse models treated with live *Bifidobacterium* species were not analyzed for side effects on organs other than the gastrointestinal tract. Also Kumar et al. did not identify the bioactive soluble factors secreted by the bacteria. However, their study has the potential to promote research in animal models of diarrhea associated with bacterial/viral pathogens or intestinal inflammation and will reinforce the use of *Bifidobacterium* formulations as antidiarrheal probiotic agents. Overall, the study strongly suggests that upregulation of DRA expression by bioactive factors secreted by *Bifidobacterium* may play an important role in treating diarrhea. The use of probiotic bacterial formulations for treatment of infectious diarrhea among younger patients may prevent side effects (e.g., nausea and loss of appetite) of traditional pharmacological drugs, thus making the use of such drugs less challenging. It is quite possible that once the signaling and bioactive factors associated with the action of a probiotic strain are evaluated, the information will give way to development of drugs that would not adversely affect the immune system in patients and would have improved efficacy during the recovery process.

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**DISCLOSURES**

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**AUTHOR CONTRIBUTIONS**

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